

HILIGHT set on as ''

? b 155, 5, 399, 72, 159, 156, 442, 444, 457, 304

>>> 457 does not exist

>>>1 of the specified files is not available

28oct02 14:21:24 User242957 Session D524.2

\$0.00 0.073 DialUnits File410

\$0.00 Estimated cost File410

\$0.43 TELNET

\$0.43 Estimated cost this search

\$0.43 Estimated total session cost 0.239 DialUnits

SYSTEM:OS - DIALOG OneSearch

File 155:MEDLINE(R) 1966-2002/Oct W3

*File 155: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.

File 5:Biosis Previews(R) 1969-2002/Oct W3

(c) 2002 BIOSIS

*File 5: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.

File 399:CA SEARCH(R) 1967-2002/UD=13717

(c) 2002 American Chemical Society

*File 399: Use is subject to the terms of your user/customer agreement. Alert feature enhanced for multiple files, etc. See HELP ALERT.

File 72:EMBASE 1993-2002/Oct W3

(c) 2002 Elsevier Science B.V.

*File 72: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.

File 159:Cancerlit 1975-2002/Sep

(c) format only 2002 Dialog Corporation

File 156:ToxFile 1965-2002/Oct W3

(c) format only 2002 The Dialog Corporation

File 442:AMA Journals 1982-2002/Oct B2

(c)2002 Amer Med Assn -FARS/DARS apply

*File 442: UD's have been adjusted to reflect the current months' data. No data is missing.

File 444:New England Journal of Med. 1985-2002/Oct W4

(c) 2002 Mass. Med. Soc.

File 304:THE MERCK INDEX ONLINE(SM) /2001Q1

(c) 2001 MERCK & CO. INC.

Set Items Description

? s putrescine or (diamino and butane)

19762 PUTRESCINE

15814 DIAMINO

30109 BUTANE

S1 19864 PUTRESCINE OR (DIAMINO AND BUTANE)

? s putrescine

S2 19762 PUTRESCINE

? s s2 and py<2001

Processing

Processing

>>>One or more prefixes are unsupported

>>> or undefined in one or more files.

19762 S2

46725912 PY<2001

S3 18544 S2 AND PY<2001

? s s3 and eif5a

18544 S3

135 EIF5A

S4 8 S3 AND EIF5A

? rd

>>>Duplicate detection is not supported for File 304.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
S5 4 RD (unique items)
? t s5/3,ab/all
>>>No matching display code(s) found in file(s): 304

5/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10993903 20558097 PMID: 11104695

Human deoxyhypusine synthase: interrelationship between binding of NAD and substrates.

Lee C H; Park M H
Building 30, Room 211, Oral and Pharyngeal Cancer Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892-4340, USA.

Biochemical journal (ENGLAND) Dec 15 2000, 352 Pt 3 p851-7,
ISSN 0264-6021 Journal Code: 2984726R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Deoxyhypusine synthase catalyses the NAD-dependent transfer of the butylamine moiety from the polyamine, spermidine, to a specific lysine residue of a single cellular protein, eukaryotic translation-initiation factor 5A (eIF5A) precursor. The native enzyme exists as a tetramer of four identical subunits and contains four binding sites for NAD. The binding of spermidine and NAD was studied by a filtration assay. [(3)H]Spermidine binding to the enzyme was not detectable alone or in the presence of the eIF5A precursor, but was detected only in the presence of NAD or NADH, suggesting that a NAD/NADH-induced conformational change is required for the binding of spermidine. A strong NAD-dependent binding was also observed with a spermidine analogue, N(1)-guanyl-1, 7-diamino[(3)H]heptane (GC(7)), but not with [(14)C]putrescine or [(14)C]spermine. Although [(3)H]NAD binding to the enzyme occurred in the absence of spermidine, its affinity for the enzyme was markedly enhanced by spermidine, GC(7) and also by the eIF5A precursor. The maximum binding for NAD and spermidine was estimated to be approximately 4 molecules each/enzyme tetramer. The dependence of spermidine binding on NAD and the modulation of binding of NAD by spermidine and the eIF5A precursor suggest intricate relationships between the binding of cofactor and the substrates, and provide new insights into the reaction mechanism.

5/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10487785 20011401 PMID: 10542236

Deoxyhypusine synthase from tobacco. cDNA isolation, characterization, and bacterial expression of an enzyme with extended substrate specificity.

Ober D; Hartmann T
Institut für Pharmazeutische Biologie der Technischen Universität Braunschweig, Mendelssohnstrasse 1, D-38106 Braunschweig, Germany.

Journal of biological chemistry (UNITED STATES) Nov 5 1999, 274

(45) p32040-7, ISSN 0021-9258 Journal Code: 2985121R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Deoxyhypusine synthase catalyzes the formation of a deoxyhypusine residue in the translation eukaryotic initiation factor 5A (eIF5A) precursor protein by transferring an aminobutyl moiety from spermidine onto a conserved lysine residue within the eIF5A polypeptide chain. This reaction commences the activation of the initiation factor in fungi and

vertebrates. A mechanistically identical reaction is known in the biosynthetic pathway leading to pyrrolizidine alkaloids in plants. Deoxyhypusine synthase from tobacco was cloned and expressed in active form in *Escherichia coli*. It catalyzes the formation of a deoxyhypusine residue in the tobacco **eIF5A** substrate as shown by gas chromatography coupled with a mass spectrometer. The enzyme also accepts free **putrescine** as the aminobutyl acceptor, instead of lysine bound in the **eIF5A** polypeptide chain, yielding homospermidine. Conversely, it accepts homospermidine instead of spermidine as the aminobutyl donor, whereby the reactions with **putrescine** and homospermidine proceed at the same rate as those involving the authentic substrates. The conversion of deoxyhypusine synthase-catalyzed **eIF5A** deoxyhypusinylation pinpoints a function for spermidine in plant metabolism. Furthermore, and quite unexpectedly, the substrate spectrum of deoxyhypusine synthase hints at a biochemical basis behind the sparse and skew occurrence of both homospermidine and its pyrrolizidine derivatives across distantly related plant taxa.

5/3,AB/3 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08823186 BIOSIS NO.: 199395112537

Effects of chronic 5'-((Z)-4-amino-2-butenyl)methylamino-5'-deoxyadenosine (AbeAdo) treatment on polyamine and eIF-5A metabolism in AbeAdo-sensitive and -resistant L1210 murine leukaemia cells.

AUTHOR: Byers Timothy L(a); Wiest Laurie; Wechter Rita S; Pegg Anthony E
AUTHOR ADDRESS: (a)Dep. Cellular Mol. Physiol., M.S. Hershey Med. Cent., Hershey, PA 17033**azakhstan

JOURNAL: Biochemical Journal 290 (1):p115-121 1993

ISSN: 0264-6021

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: We have previously reported that prolonged chronic exposure to the S-adenosyl-L-methionine decarboxylase (AdoMetDC) inhibitor, 5'-((Z)-4-amino-2-butenyl)methylamino-5'-deoxyadenosine (MDL 73811, AbeAdo), leads to cytostasis of L1210 cells (Byers, Ganem and Pegg (1992) *Biochem. J.* 287, 717-724). Further studies to investigate the mechanism by which these effects are brought about were carried out by comparing an L1210-derived cell line (R20) that is resistant to AbeAdo with the parent cells. The R20 cells were derived by two rounds of AbeAdo-induced cytostasis followed by rescue with exogenous polyamines. Cytostasis was induced in L1210 cells treated for 12 days with 10 μ M AbeAdo; however, exposure to up to 40 μ M AbeAdo did not induce cytostasis in R20 cells. **Putrescine** levels were elevated and spermine levels were depleted in both treated L1210 and treated R20 cells. Spermidine was depleted in treated L1210 cells but was only partly reduced in treated R20 cells. AdoMetDC activity was below the limit of detection in treated L1210 cells but, although greatly reduced, could be measured in the treated R20 cells. The resistance of the R20 cells to the effects of AbeAdo on cell growth and spermidine depletion correlated with reduced AbeAdo accumulation by R20 cells. In the absence of spermidine synthesis, unhyposinated eukaryotic translation initiation factor 5A (**eIF5A**) accumulated in AbeAdo-treated L1210 cells. There was no detectable accumulation of unhyposinated eIF-5A in R20 cells. Unhyposinated eIF-5A accumulated during AbeAdo treatment was depleted in L1210 cells rescued by exogenous spermidine. These findings are consistent with the hypothesis that AbeAdo-induced cytostasis is due to the loss of hyposinated eIF-5A. However, spermine was able to rescue AbeAdo-treated L1210 cells without significantly reducing the unhyposinated eIF-5A accumulated during AbeAdo treatment, suggesting that only a small amount

of the unmodified protein must be hypusinated to restore cell growth.
1993

5/3,AB/4 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2002 Elsevier Science B.V. All rts. reserv.

10966053 EMBASE No: 2001010661

Human deoxyhypusine synthase: Interrelationship between binding of NAD and substrates

Chang Hoon Lee; Park M.H.

M.H. Park, Oral and Pharyngeal Cancer Branch, Natl. Inst. of Dent./Craniofac. Res., National Institutes of Health, Bethesda, MD 20892-4340 United States

AUTHOR EMAIL: mhpark@nih.gov

Biochemical Journal (BIOCHEM. J.) (United Kingdom) 15 DEC 2000, 352/3 (851-857)

CODEN: BIJOA ISSN: 0264-6021

DOCUMENT TYPE: Journal ; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 36

Deoxyhypusine synthase catalyses the NAD-dependent transfer of the butylamine moiety from the polyamine, spermidine, to a specific lysine residue of a single cellular protein, eukaryotic translation-initiation factor 5A (**eIF5A**) precursor. The native enzyme exists as a tetramer of four identical subunits and contains four binding sites for NAD. The binding of spermidine and NAD was studied by a filtration assay. [SUP3H]Spermidine binding to the enzyme was not detectable alone or in the presence of the **eIF5A** precursor, but was detected only in the presence of NAD or NADH, suggesting that a NAD/NADH-induced conformational change is required for the binding of spermidine. A strong NAD-dependent binding was also observed with a spermidine analogue, NSUP1-guanyl-1,7-diamino[SUP3H]heptane (GCSUB7), but not with [SUP14C] **putrescine** or [SUP14C]spermine. Although [SUP3H]NAD binding to the enzyme occurred in the absence of spermidine, its affinity for the enzyme was markedly enhanced by spermidine, GCSUB7 and also by the **eIF5A** precursor. The maximum binding for NAD and spermidine was estimated to be (approximate) 4 molecules each/enzyme tetramer. The dependence of spermidine binding on NAD and the modulation of binding of NAD by spermidine and the **eIF5A** precursor suggest intricate relationships between the binding of cofactor and the substrates, and provide new insights into the reaction mechanism.

ds

Set	Items	Description
S1	19864	PUTRESCINE OR (DIAMINO AND BUTANE)
S2	19762	PUTRESCINE
S3	18544	S2 AND PY<2001
S4	8	S3 AND EIF5A
S5	4	RD (unique items)

? s s2 and py>2001

>>>One or more prefixes are unsupported

>>> or undefined in one or more files.

	19762	S2
	1467300	PY>2001
S6	462	S2 AND PY>2001

? s s6 and eif5a

	462	S6
	135	EIF5A
S7	4	S6 AND EIF5A

? rd

>>>Duplicate detection is not supported for File 304.

>>>Records from unsupported files will be retained in the RD set.

...completed examining records

S8	1	RD (unique items)
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? t s8/3,ab/all

>>>No matching display code(s) found in file(s): 304

8/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13243674 21961438 PMID: 11964177

Inhibition of cell growth through inactivation of eukaryotic translation initiation factor 5A (**eIF5A**) by deoxyspergualin.

Nishimura Kazuhiro; Ohki Yuji; Fukuchi-Shimogori Tomomi; Sakata Kaori; Saiga Kan; Beppu Takanobu; Shirahata Akira; Kashiwagi Keiko; Igarashi Kazuei

Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan.

Biochemical Journal (England) May 1 2002, 363 (Pt 3) p761-8,

ISSN 0264-6021 Journal Code: 2984726R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The mechanism of inhibition of cell growth by deoxyspergualin was studied using mouse mammary carcinoma FM3A cells. Results of studies using deoxyspergualin analogues showed that both the guanidinoheptanate amide and glyoxyspermidine moieties of deoxyspergualin were necessary to cause inhibition of cell growth. When deoxyspergualin was added to the medium, there was a strong inhibition of cell growth and formation of active eukaryotic translation initiation factor 5A (**eIF5A**) at the third day of culture. There was also a marked decrease in cellular **putrescine** content and a small decrease in spermidine content. Accumulation of decapped mRNA, which is typically associated with **eIF5A** deficiency in yeast, was also observed. The inhibition of cell growth and the formation of active **eIF5A** was not reversed by addition of spermidine. The activity of deoxyhypusine synthase, the first enzyme in the formation of active **eIF5A**, was inhibited by deoxyspergualin in a cell-free system. These results, taken together, indicate that inhibition of active **eIF5A** formation is strongly involved in the inhibition of cell growth by deoxyspergualin.

? ds

Set	Items	Description
S1	19864	PUTRESCINE OR (DIAMINO AND BUTANE)
S2	19762	PUTRESCINE
S3	18544	S2 AND PY<2001
S4	8	S3 AND EIF5A
S5	4	RD (unique items)
S6	462	S2 AND PY>2001
S7	4	S6 AND EIF5A
S8	1	RD (unique items)

? s s3 and (administer? or treat?)

Processing

	18544	S3
	652293	ADMINISTER?
	5929692	TREAT?
S9	4426	S3 AND (ADMINISTER? OR TREAT?)

? s s9 and apoptosis?

	4426	S9
	288987	APOPTOSIS?
S10	148	S9 AND APOPTOSIS?

? rd

>>>Duplicate detection is not supported for File 304.

>>>Records from unsupported files will be retained in the RD set.

...examined 50 records (50)
...examined 50 records (100)
...completed examining records
S11 49 RD (unique items)

? t s11/3,ab/all

>>>No matching display code(s) found in file(s): 304

11/3,AB/1 (Item 1 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11016921 21011385 PMID: 11128555

Inhibition of ornithine decarboxylase by alpha-difluoromethylornithine induces **apoptosis** of HC11 mouse mammary epithelial cells.

Ploszaj T; Motyl T; Zimowska W; Skierski J; Zwierzchowski L
Department of Animal Physiology, Faculty of Veterinary Medicine, Warsaw
Agricultural University, Poland. ploszaj@alpha.sggw.waw.pl
Amino acids (Austria) 2000, 19 (2) p483-96, ISSN 0939-4451
Journal Code: 9200312

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The effect of α -difluoromethylornithine (DFMO) on the **apoptosis** of HC11 mouse mammary epithelial cells was investigated. The involvement of reactive oxygen species (ROS) and Bcl-2 protein in the mechanism of **apoptosis** induced by ornithine decarboxylase (ODC) inhibition was also assessed. DFMO (0.1, 1 and 5mM) induced **apoptosis** of HC11 cells in dose- and time-dependent manner. **Apoptosis** manifests itself with morphological features like: cell shrinkage, condensation of chromatin, pyknosis and fragmentation of nucleus, followed by secondary necrosis (putrosis). The decrease in the nuclear DNA contents appearing as the hypodiploidal peak sub-G1 in the DNA histogram was not dependent on the presence of prolactin (5 microg/ml) in DFMO-treated cultures. **Apoptosis** induced by ODC inhibition was associated with a rapid increase in ROS concentration in HC11 cells observed within 1 h after DFMO treatment. The down-regulation of Bcl-2 as a decrease in cell number expressing bcl-2 and a lowered Bcl-2 protein content in cells expressing this protooncogene was also noted. The administration of **putrescine** (50 microM) lowered the number of early-apoptotic, late-apoptotic and

necrotic cells. Moreover, it increased the number of cells expressing bcl-2. In conclusion, the disturbance of cellular polyamine homeostasis by inhibition of their synthesis enhances mammary epithelial cell susceptibility to **apoptosis**. It may occur in the mammary gland at the end of lactation, when the depletion of circulating lactogenic hormones and activation of intra-mammary apoptogenic factors expression take place.

11/3,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11004858 20575781 PMID: 11133803

Apoptosis induced by 1'-acetoxychavicol acetate in Ehrlich ascites tumor cells is associated with modulation of polyamine metabolism and caspase-3 activation.

Moffatt J; Hashimoto M; Kojima A; Kennedy D O; Murakami A; Koshimizu K; Ohigashi H; Matsui-Yuasa I

Department of Food and Nutrition, Faculty of Human Life Science, Osaka, City University, Osaka 558-8585, Japan.

Carcinogenesis (ENGLAND) Dec 2000, 21 (12) p2151-7, ISSN 0143-3334 Journal Code: 8008055

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The efficacy of the antitumor activity of 1'-acetoxychavicol acetate (ACA), reported to be a suppressor of chemically induced carcinogenesis, was evaluated in Ehrlich ascites tumor cells. ACA treatment resulted in changes in morphology and a dose-dependent suppression of cell viability. **Apoptosis**, characterized by nuclear condensation, membrane blebbing, cell shrinkage and a significant induction of caspase-3-like protease activity at 8 h in a time-course study were observed. Formation of apoptotic bodies was preceded by lowering of intracellular polyamines, particularly **putrescine**, and both dose- and time-dependent inhibitory and activation effect by ACA on ornithine decarboxylase (ODC) and spermidine/spermine N(1)-acetyltransferase (SSAT), respectively. Administration of exogenous polyamines prevented ACA-induced **apoptosis** represented by a reduction in the number of apoptotic bodies and also caused reduction in the induced caspase-3-like protease activity at 8 h. These findings suggest that the anticarcinogenic effects of ACA might be partly due to perturbation of the polyamine metabolic pathway and triggering of caspase-3-like activity, which result in **apoptosis**.

11/3,AB/3 (Item 3 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10994640 20566564 PMID: 11114236

Changes in polyamine metabolism during glucocorticoid-induced programmed cell death in mouse thymus.

Hegardt C; Andersson G; Oredsson S M

Department of Animal Physiology, Lund University, Lund, Sweden.
Cecilia.Hegardt@zoofys.lu.se

Cell biology international (ENGLAND) 2000, 24 (12) p871-80,
ISSN 1065-6995 Journal Code: 9307129

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

When mice are injected with dexamethasone, cortical thymocytes are deleted through programmed cell death (PCD). We have used this in vivo model system to investigate the kinetics of PCD and cell proliferation in relation to polyamine metabolism for 16 h after injection of dexamethasone.

As a marker for PCD, we used the appearance of a sub-G(1)peak in the DNA histogram. When a sub-G(1)peak appeared at 4 h after dexamethasone treatment, the activity of the polyamine catabolic enzyme spermidine/spermine N(1)-acetyltransferase (SSAT) was significantly increased and the activity of the polyamine biosynthetic enzyme S-adenosylmethionine decarboxylase (AdoMetDC) was significantly decreased compared to the activities found in the thymi of control mice. Despite the significant changes in the activities of SSAT and AdoMetDC, the only change in the polyamine pool during the experimental period was that of **putrescine**. Presumably the complexity of this in vivo system masks changes in the spermidine and spermine pools that were expected in relation to the increased SSAT activity and decreased AdoMetDC activity. Copyright 2000 Academic Press.

11/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10849467 20400165 PMID: 10940513
Anti-proliferative effect of resveratrol, a natural component of grapes and wine, on human colonic cancer cells.

Schneider Y; Vincent F; Duranton B; Badolo L; Gosse F; Bergmann C; Seiler N; Raul F

ULP/CJF INSERM 95-09, Laboratory of Metabolic and Nutritional Control in Digestive Oncology, IRCAD, 1 Place de l'Hopital, 67091, Strasbourg, France. Cancer letters (IRELAND) Sep 29 2000, 158 (1) p85-91, ISSN

0304-3835 Journal Code: 7600053

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Resveratrol, a natural polyphenolic phytoalexine present in grapes and wines, has been reported to exert a variety of important pharmacological effects. We investigated the effects of resveratrol on the growth and polyamine metabolism of CaCo-2 human colon cancer cells. **Treatment** of the CaCo-2 cells with 25 microM resveratrol caused a 70% growth inhibition. The cells accumulated at the S/G2 phase transition of the cell cycle. No signs of cytotoxicity or **apoptosis** were detected. Resveratrol caused a significant decrease of ornithine decarboxylase (ODC) activity, a key enzyme of polyamine biosynthesis, which is enhanced in cancer growth. ODC inhibition resulted in the reduction of the intracellular **putrescine** content, indicating that polyamines might represent one of several targets involved in the anti-proliferative effects of resveratrol.

11/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10817432 20372494 PMID: 10911406
Anti-goitrous effect of lecithin-bound iodine in propylthiouracil treated rats.

Matsuzaki S; Ma H T; Burikhanov R B
Department of Biochemistry, Dokkyo University School of Medicine, Mibu, Tochig, Japan. matuzaki@dokkyomed.ac.jp

Endocrine regulations (CZECH REPUBLIC) Jun 2000, 34 (2) p57-63
ISSN 1210-0668 Journal Code: 9112018

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

OBJECTIVE: Excess iodine and some iodine-containing compounds are known to affect various parameters of thyroid function. Lecithin-bound iodine (LBI) is a compound which induces involution of an enlarged thyroid. LBI was tested for its ability to affect thyroid ornithine decarboxylase (ODC)

activity and **apoptosis**. METHODS: LBI was given orally to propylthiouracil-pretreated rats and the changes in ODC activity and **apoptosis** were observed. The thyroid **apoptosis** was detected by DNA laddering and flow cytometry. RESULTS: LBI suppressed the thyroid ODC activity within one hour after its administration and lowered slightly but significantly the thyroid **putrescine** levels at 3 h. The DNA cleavage ladder was evident at 3-6 h after LBI **treatment**. Propylthiouracil induced thyroid enlargement was reduced significantly at 3 days after chronic **treatment** with LBI. The thyroidal content of **putrescine** was also decreased after chronic **treatment**. These effects of LBI were essentially the same as those of excess iodide, while other iodinated compounds including amiodarone, iopanoic acid and erythrosine had no effect on the thyroid ODC activity. CONCLUSIONS: These results suggest that LBI may exert its anti-goitrous effects, consisting of the inhibition of ODC activity and **apoptosis**, in the form of inorganic iodide in vivo.

11/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10701410 20233695 PMID: 10769194

Polyamines directly induce release of cytochrome c from heart mitochondria.

Stefanelli C; Stanic I; Zini M; Bonavita F; Flamigni F; Zamboni L; Landi L; Pignatti C; Guarnieri C; Caldara C M

Dipartimento di Biochimica 'G. Moruzzi', Universita di Bologna, Via Irnerio, 48. I-40126 Bologna, Italy. cstefan@biocfarm.unibo.it

Biochemical journal (ENGLAND) May 1 2000, 347 Pt 3 p875-80,

ISSN 0264-6021 Journal Code: 2984726R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Cytochrome c release from mitochondria to the cytosol represents a critical step in **apoptosis**, correlated to the activation of the caspase cascade. In this report, we show that addition of micromolar concentrations of polyamines to isolated rat heart mitochondria induces the release of cytochrome c. Spermine, which is effective at concentrations of 10-100 micromM, is more potent than spermidine, whereas **putrescine** has no effect up to 1 mM. The release of cytochrome c caused by spermine is a rapid, saturable and selective process that is independent of mitochondria damage. Spermine, unlike polylysine, is able to release a discrete amount of cytochrome c from intact, functional mitochondria. The cytochrome c-releasing power of spermine is not affected by cyclosporin A, differently from the effect of permeability transition inducers. In a cardiac cell-free model of **apoptosis**, the latent caspase activity of cytosolic extracts from cardiomyocytes could be activated by cytochrome c released from spermine-treated heart mitochondria. These data indicate a novel mechanism of cytochrome c release from the mitochondrion, and suggest that prolonged and sustained elevation of polyamines, characteristic of some pathologies such as heart hypertrophy, could be involved in the development of **apoptosis**.

11/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10688751 20232498 PMID: 10769665

Changes in intracellular concentrations of amino acids and polyamines during the **apoptosis** of HL-60 cells.

Sakagami H; Fujiwara E; Yokote Y; Akahane K; Asano K; Kochi M; Hara E; Shirahata A

Department of Dental Pharmacology, Meikai University School of Dentistry, Saitama, Japan. sakagami@dent.meikai.ac.jp

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Possible changes in the intracellular concentrations of amino acids and polyamines were investigated during the **apoptosis** of human promyelocytic leukemic HL-60 cells. **Treatment** of HL-60 cells with sodium 5,6-benzylidene-L-ascorbate (SBA) or sodium ascorbate induced apoptotic cell death characterized by chromatin condensation, nuclear fragmentation, loss of microvilli, and production of numerous vacuoles and apoptotic bodies. The **apoptosis** was accompanied by a significant increase in the intracellular concentration of almost all neutral and basic amino acids (regardless of their polarity). On the other hand, the concentration of glutamic acid, the most abundant amino acid in the cells, was significantly reduced. These data suggest the reduced amino acid utilization and possible membrane impairment, especially in SBA-treated cells. Among three major polyamines, the intracellular concentration of **putrescine** rapidly declined, whereas that of spermidine and spermine was almost unchanged during **apoptosis**. Conversely, the concentration of **putrescine**, but not that of spermidine and spermine, was significantly increased during the chemically-induced carcinogenesis of mouse liver tissue. The present study demonstrates that the **putrescine** level is the most sensitive to the proliferation capability of the cells, among three polyamines, and provides an early marker for **apoptosis** and proliferation.

11/3,AB/8 (Item 8 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10649509 20178142 PMID: 10712236

Polyamine depletion delays **apoptosis** of rat intestinal epithelial cells.

Ray R M; Viar M J; Yuan Q; Johnson L R

Department of Physiology, College of Medicine, University of Tennessee, Memphis, Memphis, Tennessee 38163, USA. rray@physiol.utmem.edu

American journal of physiology. Cell physiology (UNITED STATES) Mar 2000, 278 (3) pC480-9, ISSN 0363-6143 Journal Code: 100901225

Contract/Grant No.: DK-16505; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The polyamines spermidine, spermine, and their precursor **putrescine** are essential for cell growth and the regulation of the cell cycle. Recent studies suggest that excessive accumulation of polyamines favors either malignant transformation or **apoptosis**, depending on the cell type and the stimulus. This study examines the involvement of polyamines in the induction of **apoptosis** by the DNA topoisomerase I inhibitor, camptothecin. In IEC-6 cells, camptothecin induced **apoptosis** within 6 h, accompanied by detachment of cells. Detached cells showed DNA laddering and caspase 3 induction, characteristic features of **apoptosis**. Depletion of **putrescine**, spermidine, and spermine by DL-alpha-difluoromethylornithine (DFMO), a specific inhibitor of ornithine decarboxylase (ODC) that is the first rate-limiting enzyme for polyamine biosynthesis, decreased the apoptotic index. Delayed **apoptosis** was accompanied by a decrease in caspase 3 activity in polyamine-depleted cells. Addition of **putrescine** restored the induction of **apoptosis** as indicated by an increase in the number of detached cells and caspase 3 activity. Polyamine depletion did not change the level of caspase 3 protein. Inhibition of S-adenosylmethionine decarboxylase by a specific inhibitor [diethylglyoxal bis-(guanyldrazone); DEGBG] led to

depletion of spermidine and spermine with a significant accumulation of **putrescine** and induction of ODC. The DEGBG-treated cells showed an increase in **apoptosis**, suggesting the importance of **putrescine** in the apoptotic process. Addition of **putrescine** to DFMO-treated cell extracts did not increase caspase 3 activity. The above results indicate that polyamine depletion delays the onset of **apoptosis** in IEC-6 cells and confers protection against DNA damaging agents, suggesting that polyamines might be involved in the caspase activating signal cascade.

11/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10571044 20110525 PMID: 10646605

Uptake of apoptotic cells drives the growth of a pathogenic trypanosome in macrophages.

Freire-de-Lima C G; Nascimento D O; Soares M B; Bozza P T; Castro-Faria-Neto H C; de Mello F G; DosReis G A; Lopes M F

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Nature (ENGLAND) Jan 13 2000, 403 (6766) p199-203, ISSN 0028-0836 Journal Code: 0410462

Erratum in Nature 2000 Apr 20;404(6780) 904

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

After **apoptosis**, phagocytes prevent inflammation and tissue damage by the uptake and removal of dead cells. In addition, apoptotic cells evoke an anti-inflammatory response through macrophages. We have previously shown that there is intense lymphocyte **apoptosis** in an experimental model of Chagas' disease, a debilitating cardiac illness caused by the protozoan Trypanosoma cruzi. Here we show that the interaction of apoptotic, but not necrotic T lymphocytes with macrophages infected with T. cruzi fuels parasite growth in a manner dependent on prostaglandins, transforming growth factor-beta (TGF-beta) and polyamine biosynthesis. We show that the vitronectin receptor is critical, in both apoptotic-cell cytoadherence and the induction of prostaglandin E2/TGF-beta release and ornithine decarboxylase activity in macrophages. A single injection of apoptotic cells in infected mice increases parasitaemia, whereas **treatment** with cyclooxygenase inhibitors almost completely ablates it in vivo. These results suggest that continual lymphocyte **apoptosis** and phagocytosis of apoptotic cells by macrophages have a role in parasite persistence in the host, and that cyclooxygenase inhibitors have potential therapeutic application in the control of parasite replication and spread in Chagas' disease.

11/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10519685 20054779 PMID: 10581530

Modulation of tumor cell proliferation and **apoptosis** by polyamine depletion in cells of head and neck squamous cell carcinomas.

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Radiation research (UNITED STATES) Dec 1999, 152 (6) p604-10, ISSN 0033-7587 Journal Code: 0401245

Contract/Grant No.: CA 66786; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

These studies were carried out to examine the capacity of alpha-difluoromethylornithine (DFMO) to modulate cell proliferation and **apoptosis** in cells of squamous cell carcinomas (SCCs) of the head and neck. Exposure of cells to DFMO (5 mM for 48 h) depleted intracellular **putrescine** and spermidine levels (greater than 5-fold) and inhibited proliferation of the cells without manifestation of cytotoxicity as measured by a clonogenic assay. Exposure of the cells to DFMO did not influence the survival response after exposure to single-dose radiation between 0 and 10 Gy. **Treatment** of polyamine-depleted cells with 200 nM staurosporine amplified **apoptosis** 65% (1.65-fold) over that in controls, as determined by flow cytometry. The increased **apoptosis** after DFMO **treatment** was effectively inhibited by the addition of 1 mM **putrescine** or spermidine. Cleavage of poly(ADP-ribose) polymerase (PARP) illustrated that the staurosporine **treatment** induced **apoptosis** in the cells within 6 h. Analysis of PARP cleavage indicated that **treatment** with DFMO accelerated the kinetics of progression of **apoptosis** but did not influence the sensitivity of cells to 10 nM-1 microM staurosporine. These data suggest an involvement of endogenous polyamines in modulation of proliferation kinetics and **apoptosis** in human SCCs and suggest opportunities to explore new therapeutic strategies in head and neck cancer patients to be **treated** with radiation therapy.

11/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10471399 20004016 PMID: 10535358

The c-myc gene regulates the polyamine pathway in DMSO-induced **apoptosis**.

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Cell proliferation (ENGLAND) Apr-Jun 1999, 32 (2-3) p119-29,
ISSN 0960-7722 Journal Code: 9105195

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

It is accepted that **apoptosis** is a gene-controlled process of cellular self-destruction. It occurs during physiological regulation and in pathological situations in the life of a cell. In the immune system, several different intracellular and extracellular factors have been associated with the induction of **apoptosis**, and the final responses depend on the cell system and the acquired signals. In lymphoid cells, dexamethasone-induced **apoptosis** is associated with c-myc downregulation in cells that remain in G0-G1 until the point of death. Ornithine decarboxylase (ODC), a key enzyme involved in polyamine biosynthesis, is regulated by c-myc, which is a transcriptional activator implicated not only in the control of cell proliferation and differentiation but also in programmed cell death. As dimethylsulphoxide (DMSO) induces **apoptosis** in the RPMI-8402 human pre-T cell line, the present study analysed the involvement of the c-myc proto-oncogene and polyamine pathway as mediators of **apoptosis**. Cell growth, programmed cell death, c-myc expression, ODC activity and intracellular polyamine content were detected after DMSO and difluoromethylornithine (DFMO) **treatment**. DMSO-treated cells exhibit a decrease in ODC activity and polyamine levels associated with cell growth arrest and programmed cell death induction. The expression of c-myc proto-oncogene, as its mRNA or protein, is specifically down-regulated. DFMO, a well defined polyamine biosynthesis inhibitor, completely blocks ODC activity, resulting in growth inhibition but not **apoptosis**. Moreover, in these samples no evidence of changes of c-myc expression were found. The results obtained

suggest that, in RPMI-8402 cells, DMSO provokes a c-myc-dependent decrease of ODC activity followed by a depletion of intracellular polyamine levels, associated with programmed cell death and cell growth arrest.

11/3,AB/12 (Item 12 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10454503 99446897 PMID: 10519408

The polyamine oxidase inhibitor MDL-72,527 selectively induces **apoptosis** of transformed hematopoietic cells through lysosomotropic effects.

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Memphis, Tennessee 38105, USA.

Cancer research (UNITED STATES) Oct 1 1999, 59 (19) p4944-54,
ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: CA21765; CA; NCI; CA22153; CA; NCI; DK44158; DK;
NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Polyamine oxidase functions in the polyamine catabolic pathway, converting N1-acetyl-spermidine and -spermine into **putrescine** (Put) and spermidine (Spd), respectively, thereby facilitating homeostasis of intracellular polyamine pools. Inhibition of polyamine oxidase in hematopoietic cells by a specific inhibitor, N,N'-bis(2,3-butadienyl)-1,4-butanediamine (MDL-72,527), reduces the levels of Put and Spd and induces the accumulation of N1-acetylated Spd. Although previously thought to be relatively nontoxic, we now report that this inhibitor overrides survival factors to induce cell death of several immortal and malignant murine and human hematopoietic cells, but not of primary myeloid progenitors. Cells treated with MDL-72,527 displayed biochemical changes typical of **apoptosis**, and cell death was associated with the down-regulation of the antiapoptotic protein Bcl-X(L). However, enforced overexpression of Bcl-X(L), or treatment with the universal caspase inhibitor zVAD-fmk, failed to block MDL-72,527-induced **apoptosis** in these hematopoietic cells. Despite decreases in Put and Spd pools, MDL-72,527-induced **apoptosis** was not blocked by cotreatment with exogenous Put or Spd, nor was it influenced by overexpression or inhibition of the polyamine biosynthetic enzyme ornithine decarboxylase. Significantly, MDL-72,527-induced **apoptosis** was associated with the rapid formation of numerous lysosomally derived vacuoles. Malignant leukemia cells were variably sensitive to the lysosomotropic effects of MDL-72,527, yet pretreatment with the ornithine decarboxylase inhibitor L-alpha-difluoromethylornithine sensitized all of these leukemia cells to the deleterious effects of the inhibitor by stimulating its intracellular accumulation. The lysosomotropic nature of select polyamine analogues may, thus, provide a novel chemotherapeutic strategy to selectively induce **apoptosis** of malignant hematopoietic cells.

11/3,AB/13 (Item 13 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10440929 99428472 PMID: 10497162

Polyamine regulation of plasma membrane phospholipid flip-flop during **apoptosis**.

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Journal of biological chemistry (UNITED STATES) Oct 1 1999, 274

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

During **apoptosis**, phosphatidylserine (PS) is moved from the plasma membrane inner leaflet to the outer leaflet where it triggers recognition and phagocytosis of the apoptotic cell. Although the mechanisms of PS appearance during **apoptosis** are not well understood, it is thought that declining activity of the aminophospholipid translocase and calcium-mediated, nonspecific flip-flop of phospholipids play a role. As previous studies in the erythrocyte ghost have shown that polyamines can alter flip-flop of phospholipids, we asked whether alterations in cellular polyamines in intact cells undergoing **apoptosis** would affect PS appearance, either by altering aminophospholipid translocase activity or phospholipid flip-flop. Cells of the human leukemic cell line, HL-60, were incubated with or without the ornithine decarboxylase inhibitor, difluoromethylornithine (DFMO), and induced to undergo **apoptosis** by ultraviolet irradiation. Whereas DFMO treatment resulted in profound depletion of **putrescine** and spermidine (but not spermine), it had no effect on caspase activity, DNA fragmentation, or plasma membrane vesiculation, typical characteristics of **apoptosis**. Notably, DFMO treatment prior to ultraviolet irradiation did not alter the decline in PS inward movement by the aminophospholipid translocase as measured by the uptake of 6-[(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminocaproyl] (NBD)-labeled PS detected in the flow cytometer. Conversely, the appearance of endogenous PS in the plasma membrane outer leaflet detected with fluorescein isothiocyanate-labeled annexin V and enhanced phospholipid flip-flop detected by the uptake of 1-palmitoyl-1-[6-[(7-nitro-2-1,3-benzoxadiazol-4-yl)aminocaproyl]-sn-glycero-3-phosphocholine (NBD-PC) seen during **apoptosis** were significantly inhibited by prior DFMO treatment. Importantly, replenishment of spermidine, by treatment with exogenous **putrescine** to bypass the metabolic blockade by DFMO, restored both enhanced phospholipid flip-flop and appearance of PS during **apoptosis**. Such restoration was seen even in the presence of cycloheximide but was not seen when polyamines were added externally just prior to assay. Taken together, these data show that intracellular polyamines can modulate PS appearance resulting from nonspecific flip-flop of phospholipids across the plasma membrane during **apoptosis**.

11/3,AB/14 (Item 14 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10366272 99360468 PMID: 10433086

Polyamine-fas interactions: inhibition of polyamine biosynthesis in MRL-lpr/lpr mice is associated with the up-regulation of fas mRNA in thymocytes.

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Autoimmunity (SWITZERLAND) 1999, 29 (4) p299-309, ISSN

0891-6934 Journal Code: 8900070

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

MRL-lpr/lpr is a strain of mice that develops spontaneous signs of the autoimmune disease, systemic lupus erythematosus (SLE or lupus). The lpr (lymphoproliferation) defect has been identified as an insertion of an early transposon (ETn) derived sequence into the fas **apoptosis** gene. We studied the in vivo effects of difluoromethylornithine (DFMO), an irreversible inhibitor of the polyamine biosynthetic enzyme, ornithine

decarboxylase (ODC), on the expression of fas in MRL-lpr/lpr mice as well as in congenic MRL- + / + and autoimmune NZB/W strains. Using Northern blot hybridization and reverse transcription polymerase chain reaction (RT-PCR), we found that DFMO treatment resulted in an increase in the expression of fas mRNA in the thymus of MRL-lpr/lpr mice. Using RT-PCR, we further found that the increased expression of fas was associated with the suppression of chimeric ETn/fas mRNA. With fractionated CD4 + and CD8 + T cells, we found a cell-specific effect of DFMO on chimeric ETn/fas expression in CD8 + cells. ETn/fas expression was detected in CD8+ T cells from untreated mice, but it was eliminated after DFMO treatment. HPLC analysis of polyamines showed depletion of putrescine and partial reduction of spermidine (35%) in DFMO-treated mice compared to controls. These results indicate that DFMO-mediated polyamine depletion is linked to the regulation of fas and chimeric ETn/fas in MRL-lpr/lpr mice. Elevated levels of polyamines in this strain, as found in earlier studies, may be associated with the progression of the autoimmune disease by altering the expression of fas gene or by facilitating the expression of chimeric ETn/fas. Our data also provide new mechanistic insights into the beneficial effects of DFMO on these mice.

11/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10244697 99243950 PMID: 10228944

Effects of epidermal growth factor on MDA-MB-468 breast cancer cells: alterations in polyamine biosynthesis and the expression of p21/CIP1/WAF1.

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Journal of cellular physiology (UNITED STATES) Jun 1999, 179

(3) p257-66, ISSN 0021-9541 Journal Code: 0050222

Contract/Grant No.: CA42439; CA; NCI; CA73058; CA; NCI; ES 05022; ES; NIEHS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We examined the effects of epidermal growth factor (EGF) on MDA-MB-468 cells to understand its mechanism of action in an EGF receptor-rich breast cancer cell line. EGF inhibited the growth of MDA-MB-468 cells with an IC50 of 1.5 +/- 0.5 nM, as determined by measurements of DNA content of cells in culture over a period of 4 to 6 days. This growth inhibition included apoptosis 24 h after EGF addition, as detected by an enzyme-linked immunosorbent assay (ELISA) and Hoechst 33342 staining. In EGF-treated cells, peak activities of two key enzymes of polyamine biosynthesis, ornithine decarboxylase (ODC) and S-adenosylmethionine decarboxylase (SAMDC), were reduced by 57% and 83%, respectively. EGF treatment also caused a 30 to 50% decrease in cellular putrescine at all time points tested (12 to 48 h). EGF-induced inhibition of DNA synthesis was also partially reversed by the addition of putrescine or spermidine, but not by spermine. Western blot analysis of cell cycle regulatory proteins showed that EGF-mediated growth inhibition was associated with the induction of p21, an inhibitor of cyclin-dependent kinases. However, EGF had no significant effect on the expression of cyclin D1 or cyclin E. Furthermore, putrescine reversal of EGF effects was associated with the down-regulation of EGF-induced p21. These results suggest that the mechanism of growth inhibition by EGF in MDA-MB-468 cells include a down-regulation of polyamine biosynthesis and the induction of p21. Identification of growth regulatory pathways in breast cancer cells might be useful in the development of novel targets for

therapeutic intervention.

11/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10231069 99221937 PMID: 10203604

Growth inhibition of human osteosarcoma HuO9 cells by methylglyoxal bis(cyclopentylamidino)hydrazine in vitro and in vivo.

Sato N; Hibasami H; Mori K; Kaneko H; Wakabayashi H; Hirata K; Sonoda J; Nakashima K; Uchida A

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Oncology reports (GREECE) May-Jun 1999, 6 (3) p627-30, ISSN 1021-335X Journal Code: 9422756

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Polyamines are considered to be important intracellular molecules for the proliferation of cancer cells. In this study, effects of methyl-glyoxal bis(cyclopentylamidino)hydrazine (MGBCP), a potent inhibitor of the polyamine biosynthetic pathway, on the growth of human osteosarcoma HuO9 cells have been investigated. MGBCP dose-dependently inhibited the growth of HuO9 cells, in which the contents of spermine, spermidine and **putrescine** decreased concomitantly. The MGBCP-treated cells clearly exhibited morphological changes, indicating the blebbing and chromatin condensation which are characteristic of **apoptosis**. Characteristic oligonucleosomal-sized DNA fragments were observed in the MGBCP-treated cells. In vivo experiments MGBCP (20 or 50 mg/kg) inhibited the growth of transplanted HuO9 tumors in mice. These findings suggest that the inhibition of polyamine synthesis results in the suppression of growth of osteosarcoma HuO9 cells, eventually inducing **apoptosis** in these human osteosarcoma cells in vitro and in vivo.

11/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10230606 99210457 PMID: 10194553

Effects of methylacetylenic **putrescine**, an ornithine decarboxylase inhibitor and potential novel anticancer agent, on human and mouse cancer cell lines.

Palyi I; Kremmer T; Kalnay A; Turi G; Mihalik R; Bencsik K; Boldizsar M
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Anti-cancer drugs (ENGLAND) Jan 1999, 10 (1) p103-11, ISSN 0959-4973 Journal Code: 9100823

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Sensitivity of several human and mouse cancer cell lines to methylacetylenic **putrescine** (MAP) was evaluated using clonogenic, sulforhodamine B and cell counting assays. The effects of MAP on cell morphology, cell cycle phase distribution and changes in polyamine metabolism of xenografted MCF-7 and MDA-MB-231 human mammary tumor cells were also investigated. On the basis of IC50 values, BHT-101 human thyroid carcinoma cells were the most sensitive (9 micrograms/ml), followed by P388 mouse lymphoma (32 micrograms/ml), MCF-7 (48 micrograms/ml) and MDA-MB-231 (110 micrograms/ml) human breast carcinoma cell lines. MAP **treatment** led to accumulation of P388 cells in G1 phase. At higher doses, the cytoplasm of the cells became vacuolated followed by **apoptosis**. The foamy cytoplasm may suggest a rare type of cell death (Clarke III type)

called non-apoptotic programmed cell death. MAP treatment resulted in a total inhibition of ornithine decarboxylase (ODC) activity with a concomitant decrease of intracellular polyamine (mostly putrescine and spermidine) content in the breast cancer cells, whilst the spermine concentration was shown to increase. MAP proved at least 10 times more potent than the formerly studied DL-alpha-difluoromethylornithine making it an attractive candidate for clinical testing.

11/3,AB/18 (Item 18 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10227385 99216089 PMID: 10199827

Inhibition of polyamine synthesis induces p53 gene expression but not apoptosis.

Li L; Li J; Rao J N; Li M; Bass B L; Wang J Y
Department of Surgery, University of Maryland School of Medicine and Baltimore Veterans Affairs Medical Center, Baltimore, Maryland 21201, USA.
American journal of physiology (UNITED STATES) Apr 1999, 276 (4)
Pt 1) pC946-54, ISSN 0002-9513 Journal Code: 0370511
Contract/Grant No.: DK-45314; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The nuclear phosphoprotein p53 acts as a transcription factor and is involved in growth inhibition and apoptosis. The present study was designed to examine the effect of decreasing cellular polyamines on p53 gene expression and apoptosis in small intestinal epithelial (IEC-6) cells. Cells were grown in DMEM containing 5% dialyzed fetal bovine serum in the presence or absence of alpha-difluoromethylornithine (DFMO), a specific inhibitor of polyamine biosynthesis, for 4, 6, and 12 days. The cellular polyamines putrescine, spermidine, and spermine in DFMO-treated cells decreased dramatically at 4 days and remained depleted thereafter. Polyamine depletion by DFMO was accompanied by a significant increase in expression of the p53 gene. The p53 mRNA levels increased 4 days after exposure to DFMO, and the maximum increases occurred at 6 and 12 days after exposure. Increased levels of p53 mRNA in DFMO-treated cells were paralleled by increases in p53 protein. Polyamines given together with DFMO completely prevented increased expression of the p53 gene. Increased expression of the p53 gene in DFMO-treated cells was associated with a significant increase in G1 phase growth arrest. In contrast, no features of programmed cell death were identified after polyamine depletion: no internucleosomal DNA fragmentation was observed, and no morphological features of apoptosis were evident in cells exposed to DFMO for 4, 6, and 12 days. These results indicate that 1) decreasing cellular polyamines increases expression of the p53 gene and 2) activation of p53 gene expression after polyamine depletion does not induce apoptosis in intestinal crypt cells. These findings suggest that increased expression of the p53 gene may play an important role in growth inhibition caused by polyamine depletion.

11/3,AB/19 (Item 19 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10194081 99170514 PMID: 10069996

Polyamine depletion arrests cell cycle and induces inhibitors p21(Waf1/Cip1), p27(Kip1), and p53 in IEC-6 cells.

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American journal of physiology (UNITED STATES) Mar 1999, 276 (3)
Pt 1) pC684-91, ISSN 0002-9513 Journal Code: 0370511

Contract/Grant No.: DK-16505; DK; NIDDK; HL-48308; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The polyamines spermidine and spermine and their precursor **putrescine** are intimately involved in and are required for cell growth and proliferation. This study examines the mechanism by which polyamines modulate cell growth, cell cycle progression, and signal transduction cascades. IEC-6 cells were grown in the presence or absence of DL-alpha-difluoromethylornithine (DFMO), a specific inhibitor of ornithine decarboxylase, which is the first rate-limiting enzyme for polyamine synthesis. Depletion of polyamines inhibited growth and arrested cells in the G1 phase of the cell cycle. Cell cycle arrest was accompanied by an increase in the level of p53 protein and other cell cycle inhibitors, including p21(Waf1/Cip1) and p27(Kip1). Induction of cell cycle inhibitors and p53 did not induce **apoptosis** in IEC-6 cells, unlike many other cell lines. Although polyamine depletion decreased the expression of extracellular signal-regulated kinase (ERK)-2 protein, a sustained increase in ERK-2 isoform activity was observed. The ERK-1 protein level did not change, but ERK-1 activity was increased in polyamine-depleted cells. In addition, polyamine depletion induced the stress-activated protein kinase/c-Jun NH2-terminal kinase (JNK) type of mitogen-activated protein kinase (MAPK). Activation of JNK-1 was the earliest event; within 5 h after DFMO treatment, JNK activity was increased by 150%. The above results indicate that polyamine depletion causes cell cycle arrest and upregulates cell cycle inhibitors and suggest that MAPK and JNK may be involved in the regulation of the activity of these molecules.

11/3,AB/20 (Item 20 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10120600 99074508 PMID: 9852627

Involvement of **apoptosis** and cyclin D1 gene repression in growth inhibition of T-47D human breast cancer cells by methylglyoxal bis(cyclopentylamidino)hydrazine).

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International journal of molecular medicine (GREECE) Jun 1998, 1

(6) p931-6, ISSN 1107-3756 Journal Code: 9810955

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Polyamines are considered to be important intracellular molecules for the proliferation of the cancer cells. In this study, effects of methylglyoxal bis(cyclopentylamidino)hydrazine) (MGBCP), a potent inhibitor of the polyamine biosynthetic pathway, on the growth and cell cycle of T-47D human breast cancer cells were investigated. MGBCP dose-dependently inhibited the growth of T-47D cells, in which the contents of spermine, spermidine and **putrescine** decreased concomitantly. The gene expression of cyclin D1 was also repressed by the MGBCP treatment. The MGBCP-treated cells clearly exhibited morphological changes indicating the blebbing and chromatin condensation which are characteristic of **apoptosis**. Flow cytometric analysis showed hypo-diploid subpopulations due to apoptotic cells, and characteristic oligonucleosomal-sized DNA fragments were clearly observed for MGBCP-treated cells as the concentration of the drug was increased. These findings suggest that the inhibition of polyamine synthesis results in the repressions of cyclin D1 expression and cell cycle progression, eventually inducing **apoptosis** in these human breast cancer cells.

11/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10071899 99065321 PMID: 9850069

Alpha-difluoromethylornithine inhibits N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in zinc-deficient rats: effects on esophageal cell proliferation and **apoptosis**.

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Cancer research (UNITED STATES) Dec 1 1998, 58 (23) p5380-8,

ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: GM-26290; GM; NIGMS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Sustained, increased cell proliferation induced by dietary zinc deficiency in rats plays a critical role in esophageal carcinogenesis. It is the determining factor that converts an otherwise nontumorigenic dose of N-nitrosomethylbenzylamine (NMBA) into a highly tumorigenic one. We studied whether the increased esophageal cell proliferation and susceptibility to NMBA-induced carcinogenesis induced by zinc deficiency can be inhibited by alpha-difluoromethylornithine (DFMO), an enzyme-activated, irreversible inhibitor of ornithine decarboxylase (the first enzyme in polyamine synthesis). Weanling rats were divided into four groups: Zn+/DFMO-, Zn+/DFMO+, Zn-/DFMO-, and Zn-/DFMO+. They were fed ad libitum either a zinc-sufficient (Zn+, 75 ppm zinc) or a zinc-deficient (Zn-, 4 ppm zinc) diet and given either deionized water (DFMO-) or 1% DFMO in deionized water (DFMO+). After 5 weeks, 5-19 animals from each group were sacrificed after in vivo 5-bromo-2'-deoxyuridine labeling to detect cells in S phase. The remaining animals in each group were given a single intragastric dose of NMBA at 2 mg/kg and sacrificed 12 weeks later for tumor incidence analysis. At week 5, DFMO treatment greatly decreased (by 48-82%) the levels of **putrescine** and **spermidine** in rat esophagus, colon, and liver, irrespective of dietary zinc intake. The increased esophageal cell proliferation induced by dietary zinc deficiency, as measured by the labeling index, the number of labeled cells, and the total number of cells, was substantially reduced by DFMO. This was accompanied by an increase in the rate of **apoptosis**. In addition, the expression of bax protein, an **apoptosis** accelerator, was markedly stronger in esophagi from Zn-/DFMO+ animals that showed increased **apoptosis**, whereas increased expression of bcl-2, an inhibitor of **apoptosis**, was only seen in the highly proliferative, zinc-deficient esophagus (Zn-/DFMO-). At week 12 after NMBA dosing, DFMO reduced the incidence of esophageal tumors from 80 to 4% in zinc-deficient rats. Our data showed that DFMO effectively inhibited the increased esophageal cell proliferation induced by dietary zinc deficiency and reduced the incidence of esophageal tumors induced by a single dose of NMBA in zinc-deficient animals. Our results also indicate a role for increased **apoptosis** in the mechanism(s) whereby DFMO brings about the inhibition of cell proliferation and tumor induction. These findings support a role for DFMO as a chemopreventive agent.

11/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10031589 99035037 PMID: 9816189

Polyamine analogue induction of programmed cell death in human lung tumor cells.

McCloskey D E; Yang J; Woster P M; Davidson N E; Casero R A

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Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Mar 1996, 2 (3)
p441-6, ISSN 1078-0432 Journal Code: 9502500
Contract/Grant No.: CA/ES66204; CA; NCI; CA09071; CA; NCI; CA57545; CA;
NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The naturally occurring polyamines **putrescine**, spermidine, and spermine are required for cell growth. Based on this requirement, several polyamine analogues that interfere with polyamine function and metabolism have been synthesized as antineoplastic agents. The symmetrically substituted N1,N12-bis(ethyl)spermine (BESpm), and unsymmetrically substituted N1-ethyl-N11-[(cyclopropyl)methyl]-4, 8-diazaundecane (CPENSpm) have previously been shown to cause rapid cytotoxicity of NCI H157 cells, with concurrent high induction of the polyamine catabolic enzyme spermidine/spermine N1-acetyltransferase. However, the precise mechanism(s) of the cytotoxic action of the compounds is not known. We now demonstrate that **treatment** with either BESpm or CPENSpm results in morphological and biochemical changes consistent with the activation of programmed cell death pathways, and that the unsymmetrically substituted CPENSpm more rapidly activates the death program. These studies suggest that the cell type-specific cytotoxicity of these polyamine analogues may be a result of their ability to selectively activate the cell death pathway in sensitive phenotypes and indicate that the relationship between the structure of the polyamine analogues and the ability to induce programmed cell death should be investigated.

11/3,AB/23 (Item 23 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09900485 98317944 PMID: 9655238

Activation of the ornithine decarboxylase-polyamine system and induction of c-fos and p53 expression in relation to excitotoxic neuronal **apoptosis** in normal and microencephalic rats.

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Experimental brain research. Experimentelle Hirnforschung.
Experimentation cerebrale (GERMANY) Jun 1998, 120 (4) p519-26,
ISSN 0014-4819 Journal Code: 0043312

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Microencephalic rats obtained by gestational **treatment** with the DNA alkylating agent methylazoxymethanol, show a remarkable lack of sensitivity to excitotoxic neuropathology caused by systemic injections of the convulsant neurotoxin kainic acid. Taking advantage of this, we have studied in these rats, as well as in normal rats, the relationship between the induction of cellular signals supposedly related to cell death and the neuronal **apoptosis** consequent to kainic acid administration. While normal rats responded to the excitatory insult with a large and relatively long lasting increase of the activity of the enzyme ornithine decarboxylase and of the concentration of **putrescine** in some brain regions, these alterations were much smaller in microencephalic rats. Expression of c-fos in brain regions sensitive to kainic acid was quicker but lasted a noticeably shorter time in microencephalic rats as compared to normal animals. A profusion of apoptotic neurons, labeled by an in situ technique, were observed in the olfactory cortex, amygdala and hippocampus of normal

rats injected with kainic acid, in particular 48 h and 72 h after drug administration. At corresponding time intervals and with similar topographic localization, neurons expressing p53 protein were observed. By contrast, microencephalic rats displayed only in a few cases and in a small number apoptotic neurons in restricted areas of the ventral hippocampus and entorhinal cortex. Noticeably, in these cases small populations of p53-expressing neurons were also present in the same areas. The present observations clearly show that oncogenes such as c-fos and p53, as well as ornithine decarboxylase which behaves as an immediate-early gene in the brain under certain circumstances, undergo noticeably lower and/or shorter induction in microencephalic rats exposed to excitotoxic stimuli. In these rats, therefore, the cellular signalling pathways studied here and related to excitotoxic sensitivity and commitment to cell death are downregulated as a probable consequence of altered brain wiring.

11/3,AB/24 (Item 24 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09893217 98336219 PMID: 9670045

Cerebral ischemia enhances polyamine oxidation: identification of enzymatically formed 3-aminopropanal as an endogenous mediator of neuronal and glial cell death.

Ivanova S; Botchkina G I; Al-Abed Y; Meistrell M; Batliwalla F; Dubinsky J M; Iadecola C; Wang H; Gregersen P K; Eaton J W; Tracey K J

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Journal of experimental medicine (UNITED STATES) Jul 20 1998,

188 (2) p327-40, ISSN 0022-1007 Journal Code: 2985109R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

To elucidate endogenous mechanisms underlying cerebral damage during ischemia, brain polyamine oxidase activity was measured in rats subjected to permanent occlusion of the middle cerebral artery. Brain polyamine oxidase activity was increased significantly within 2 h after the onset of ischemia in brain homogenates (15.8 +/- 0.9 nmol/h/mg protein) as compared with homogenates prepared from the normally perfused contralateral side (7.4 +/- 0.5 nmol/h/mg protein) (P < 0.05). The major catabolic products of polyamine oxidase are **putrescine** and 3-aminopropanal. Although 3-aminopropanal is a potent cytotoxin, essential information was previously lacking on whether 3-aminopropanal is produced during cerebral ischemia. We now report that 3-aminopropanal accumulates in the ischemic brain within 2 h after permanent forebrain ischemia in rats. Cytotoxic levels of 3-aminopropanal are achieved before the onset of significant cerebral cell damage, and increase in a time-dependent manner with spreading neuronal and glial cell death. Glial cell cultures exposed to 3-aminopropanal undergo **apoptosis** (LD50 = 160 &mgr;M), whereas neurons are killed by necrotic mechanisms (LD50 = 90 &mgr;M). The tetrapeptide caspase 1 inhibitor (Ac-YVAD-CMK) prevents 3-aminopropanal-mediated **apoptosis** in glial cells. Finally, **treatment** of rats with two structurally distinct inhibitors of polyamine oxidase (aminoguanidine and chloroquine) attenuates brain polyamine oxidase activity, prevents the production of 3-aminopropanal, and significantly protects against the development of ischemic brain damage in vivo. Considered together, these results indicate that polyamine oxidase-derived 3-aminopropanal is a mediator of the brain damaging sequelae of cerebral ischemia, which can be therapeutically modulated.

11/3,AB/25 (Item 25 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09861986 98297958 PMID: 9632528

Sensitization of tnf-induced **apoptosis** with polyamine synthesis inhibitors in different human and murine tumour cell lines.

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Cytokine (UNITED STATES) Jun 1998, 10 (6) p423-31, ISSN 1043-4666 Journal Code: 9005353

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Rat/mouse T cell hybridoma-derived PC60 R55/R75 cells were used as a model to study tumour necrosis factor (TNF)-induced **apoptosis**. The role of ornithine decarboxylase (ODC) activity and polyamines in this process was investigated. In PC60 R55/R75 cells, TNF-induced ODC activity was completely suppressed by externally added spermine (Spm). TNF decreased the intracellular levels of the three polyamines Spm, spermidine (Spd) and **putrescine** (Put). A reduction of the intracellular [Spm] with methylglyoxal bis(quanyl hydrasone) (MGBG), CGP48644a, or bis(ethyl)norspermine (BENSpm), clearly sensitized the cells towards the apoptotic effect of TNF. Conversely, an increase in intracellular [Spm] with DFMO or externally added Spm reduced cellular sensitivity. Similar results were obtained after TNF treatment of the human cell lines Kym 39A6 (rhabdomyosarcoma), HeLaH21 (cervix carcinoma) and U937 (histiocytoma) and after alphaFas treatment of HeLaH21, U937 and CEM-CM3 (human T cell line). These results suggest that a decrease of intracellular Spm levels rather than ODC activity per se is involved in the sensitization towards **apoptosis** induced by TNF or alphaFas. Copyright 1998 Academic Press Limited.

11/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09811931 98224100 PMID: 9563003

Difluoromethylornithine antagonizes taxol cytotoxicity in MCF-7 human breast cancer cells.

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School of Life Sciences, Jawaharlal Nehru University, New Delhi, India.

Oncology research (UNITED STATES) 1997, 9 (11-12) p565-72,

ISSN 0965-0407 Journal Code: 9208097

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Taxol is a naturally occurring anticancer agent. We studied the combined effects of taxol with 0.1 mM of the ornithine decarboxylase inhibitor alpha-difluoromethylornithine (DFMO) in the MCF-7 human breast adenocarcinoma cell line. The effects of taxol on MCF-7 cells were evident at 0.05-1 microM and the half-maximum inhibition was calculated to be 0.05 microM. Although the cells in the control group continued to proliferate during an 8-day growth period, cells in the taxol-treated group showed approximately 78% inhibition on day 6 and approximately 92% inhibition on day 8. The combined effects of different concentrations of taxol with 0.1 mM DFMO for 48 h showed that DFMO reversed the cytotoxicity of taxol. The combined effects of 0.5 microM taxol and 0.1 mM DFMO over an 8-day period resulted in the reversal of taxol cytotoxicity by 74% on the sixth day of culture. Pretreatment and posttreatment with 0.1 mM DFMO protected the MCF-7 human breast adenocarcinoma cells from the cytotoxic effect of taxol. Polyamine levels were inhibited in cells treated with DFMO for 24 h. In a separate experiment, we verified that the addition

of exogenous **putrescine** along with taxol and DFMO to cultures for 48 h restored the cytotoxic effects of taxol. Following exposure to 0.5 microM taxol, over 59% of MCF-7 cells were in G2/M phase. DFMO (0.1 mM) showed only a slight increase in the G1 phase of the cell cycle. However, in cells **treated** with taxol and DFMO, there was no change in the percent of cells in the G2/M phase compared to taxol-**treated** cells. Therefore, depletion of cellular polyamines may not interfere with cell cycle changes induced by taxol. **Treatment** of MCF-7 cells with 0.5 microM taxol resulted in the fragmentation of genomic DNA, indicating **apoptosis**, whereas the combined effects of taxol with DFMO inhibited DNA fragmentation.

11/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09802590 98230433 PMID: 9570506

Tissue transglutaminase is not increased during **apoptosis** of HT-1080 human fibrosarcoma cells.

Lim S D; Bae S I; Kim I G; Park S C; Chung S I; Nomizu M; Kleinman H K; Kim W H

Department of Pathology, Seoul National University College of Medicine, Korea.

Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie (GERMANY) Mar 1998, 50

(1) p79-82, ISSN 0940-2993 Journal Code: 9208920

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Tissue transglutaminase (tTGase), a cytosolic enzyme which catalyzes the covalent cross-linking of proteins, is thought to be involved in the **apoptosis**. Here, we tested whether tTGase is involved during HT-1080 fibrosarcoma cell **apoptosis** induced by the YIGSR (Tyr-Ile-Gly-Ser-Arg) peptide. This sequence is derived from the laminin alpha1 chain, and its potency is increased by the formation of a 16mer polymerization using a lysine tree structure. Cells were **treated** with several different concentrations of Ac-Y 16 for 16 hours, and **apoptosis** was increased in dose-dependent manner. When assayed by incorporation of [14C] **putrescine** into succinylated casein, total transglutaminase activity was decreased in parallel with the change in the number of attached cells. Western blot analysis using polyclonal antibody against tTGase showed that the tTGase protein level had not been significantly changed when equal amounts of the protein were applied. To confirm this result, we induced **apoptosis** of these cells by coating the tissue culture plates with non-adhesive poly-hydroxyethyl methacrylate (HEMA). Western blot analysis showed that the tTGase protein level did not change during this process of **apoptosis**. Although it has been suggested that tTGase is involved in the process of **apoptosis** of various cells in vitro and in vivo, our data demonstrate that tTGase is not involved in the process of **apoptosis** of HT-1080 human fibrosarcoma cell induced by either Ac-Y 16 or a non-adhesive culture surface.

11/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09796884 98222942 PMID: 9563478

Polyamines regulate expression of the neoplastic phenotype in mouse skin.

Peralta Soler A; Gilliard G; Megosh L; George K; O'Brien T G

The Lankenau Medical Research Center, Wynnewood, Pennsylvania 19096, USA.

Cancer research (UNITED STATES) Apr 15 1998, 58 (8) p1654-9,

ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: ES01664; ES; NIEHS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Elevated polyamine levels are characteristic of many types of neoplastic cells and tissues. We demonstrate that in transgenic mice overexpressing ornithine decarboxylase in skin, changes in tissue polyamine levels, particularly **putrescine**, control the development and maintenance of the neoplastic phenotype. A specific inhibitor of the transgene, alpha-difluoromethylornithine (DFMO), reversibly blocked the appearance of squamous papillomas after carcinogen **treatment**. Furthermore, **treatment** of papilloma-bearing mice with DFMO caused rapid tumor regression, also in a reversible manner. Although the rate of **apoptosis** in papillomas was unaffected by acute DFMO **treatment**, tumor cell proliferation was rapidly decreased after drug **treatment**. Conversely, proliferation of normal epidermal keratinocytes was unaffected by DFMO **treatment**. The regulatory polyamine in this model appears to be **putrescine**, the immediate product of ornithine decarboxylase. These results demonstrate that elevated polyamine levels are required for both the development and maintenance of the neoplastic phenotype in skin.

11/3,AB/29 (Item 29 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09713289 98156383 PMID: 9496697

Polyamine depletion protects HL-60 cells from 2-deoxy-D-ribose-induced **apoptosis**.

Monti M G; Ghiaroni S; Pernecco L; Barbieri D; Marverti G; Franceschi C
Life sciences (ENGLAND) 1998, 62 (9) p799-806, ISSN 0024-3205

Journal Code: 0375521

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We investigated the involvement of natural polyamines in HL-60 cell death triggered by exposure to 2-deoxy-D-ribose (dRib). In contrast to previous studies, exogenous polyamines failed to protect HL-60 cells against **apoptosis** caused by dRib. Moreover, in our experimental conditions, depletion of intracellular levels of **putrescine** and spermidine by alpha-difluoromethylornithine (DFMO) delayed the onset of **apoptosis** by at least a day or so. Exogenous polyamines reversed the beneficial effect of DFMO and restored the apoptotic levels observed in dRib-**treated** cells. We suggested that polyamines, especially **putrescine** and spermidine, act as facilitating factors in the induction of **apoptosis** triggered by dRib in HL-60 cells.

11/3,AB/30 (Item 30 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09654421 98085790 PMID: 9417887

Anti-IgM-induced growth inhibition and **apoptosis** are independent of ornithine decarboxylase in Ramos cells.

Lin C K; Zou H Y; Kaptein J S; Yen C F; Kalunta C I; Nguyen T T; Park E;
Lad P M

Regional Research Laboratory, Kaiser Foundation Hospitals, Los Angeles, California 90027, USA.

Experimental cell research (UNITED STATES) Nov 25 1997, 237 (1)
p231-41, ISSN 0014-4827 Journal Code: 0373226

Contract/Grant No.: RR-0551-19; RR; NCRR

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Ornithine decarboxylase (ODC) is a key enzyme involved in polyamine production and is thought to regulate growth and **apoptosis** in multiple cell systems. A potential link between ODC and growth may involve the action of an oncogene c-myc which is thought to transcriptionally regulate ODC. We have examined the involvement of ODC in anti-IgM-induced growth inhibition and **apoptosis** in Burkitt's lymphoma cells. Inhibitors of ODC such as difluoromethylornithine (DFMO) completely blocked ODC activity, resulting in growth inhibition but not **apoptosis**. Addition of **putrescine**, the product of ODC enzymatic action, to Ramos cells had only a minor effect on growth, did not cause **apoptosis**, did not augment or block anti-IgM-mediated growth inhibition and **apoptosis**, but did reverse DFMO-mediated growth inhibition. Anti-IgM treatment of Ramos cells, which markedly decreased c-myc mRNA and protein, caused a paradoxical increase in ODC mRNA level as well as ODC enzymatic activity and increased cellular levels of **putrescine**. DFMO and **putrescine** did not alter c-myc mRNA levels directly, nor did they have any effects on anti-IgM-mediated down-regulation of c-myc mRNA. TNF-alpha, which inhibited anti-IgM-mediated **apoptosis**, did not inhibit either anti-IgM or DFMO-mediated inhibition of growth. These agents were without effect on ODC activity itself or on the anti-IgM-mediated increase in ODC activity. From these studies we conclude that ODC inhibition affects growth but is unrelated to the induction of **apoptosis**. Both anti-IgM-mediated inhibition of growth and induction of **apoptosis** are independent of ODC. Thus two distinct pathways for growth regulation are present: one in which ODC and polyamines are important and the other cell surface receptor-mediated (sIg) which is independent of ODC and polyamines.

11/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09637936 98060742 PMID: 9396730

Excess **putrescine** accumulation inhibits the formation of modified eukaryotic initiation factor 5A (eIF-5A) and induces **apoptosis**.

Tome M E; Fiser S M; Payne C M; Gerner E W

Department of Radiation Oncology, Arizona Health Sciences Center, University of Arizona, Tucson, AZ 85724, USA.

Biochemical journal (ENGLAND) Dec 15 1997, 328 (Pt 3) p847-54, ISSN 0264-6021 Journal Code: 2984726R

Contract/Grant No.: CA-23074; CA; NCI; CA-30052; CA; NCI; CA-72008; CA; NCI; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

DH23A cells, an alpha-difluoromethylornithine-resistant variant of the parental hepatoma tissue culture cells, express high levels of stable ornithine decarboxylase. Aberrantly high expression of ornithine decarboxylase results in a large accumulation of endogenous **putrescine** and increased **apoptosis** in DH23A cells when alpha-difluoromethylornithine is removed from the culture. Treatment of DH23A cells with exogenous **putrescine** in the presence of alpha-difluoromethylornithine mimics the effect of drug removal, suggesting that **putrescine** is a causative agent or trigger of **apoptosis**. Accumulation of excess intracellular **putrescine** inhibits the formation of hypusine in vivo, a reaction that proceeds by the transfer of the butylamine moiety of spermidine to a lysine residue in eukaryotic initiation factor 5A (eIF-5A). Treatment of DH23A cells with diaminoheptane, a competitive inhibitor of the post-translational modification of eIF-5A, causes both the suppression of eIF-5A modification in vivo and induction of **apoptosis**. These data support the hypothesis that rapid degradation of ornithine decarboxylase is a protective mechanism

to avoid cell toxicity from **putrescine** accumulation. Further, these data suggest that suppression of modified eIF-5A formation is one mechanism by which cells may be induced to undergo **apoptosis**.

11/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09606842 98028689 PMID: 9359869

Rapid induction of **apoptosis** by deregulated uptake of polyamine analogues.

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Biochemical journal (ENGLAND) Nov 15 1997, 328 (Pt 1) p307-16, ISSN 0264-6021 Journal Code: 2984726R

Contract/Grant No.: GM-26290; GM; NIGMS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Treatment of Chinese hamster ovary cells with alpha-difluoromethylornithine for 3 days, followed by exposure to cycloheximide, led to an unregulated, rapid and massive accumulation of polyamine analogues. This accumulation led to cell death by **apoptosis** within a few hours. Clear evidence of DNA fragmentation was seen in response to both N-terminally ethylated polyamines and to polyamines containing methyl groups on the terminal carbon atoms. Programmed cell death was induced within 2-4 h of exposure to 1 &mgr;M or higher concentrations of N1,N11-bis(ethyl)norspermine. The presence of cycloheximide increased the uptake of the polyamine analogues and therefore led to cell death at lower analogue concentrations, but it was not essential for the induction of **apoptosis**, since similar effects were seen when the protein synthesis inhibitor was omitted and the concentration of N1, N11-bis(ethyl)norspermine was increased to 5 microM or more. The induction of **apoptosis** was blocked both by the addition of the caspase inhibitor N-benzoyloxycarbonyl-Val-Ala-Asp-fluoromethylketone, or by the addition of the polyamine oxidase inhibitor N1-methyl-N2-(2,3-butadienyl)butane-1,4-diamine (MDL 72,527). These experiments provide evidence to support the concepts that: (1) polyamines or their oxidation products may be initiators of programmed cell death; (2) regulation of polyamine biosynthesis and uptake prevents the accumulation of toxic levels of polyamines; and (3) the anti-neoplastic effects of bis(ethyl) polyamine analogues may be due to the induction of **apoptosis** in sensitive tumour cells.

11/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09573887 97462218 PMID: 9316488

N-acetylcysteine does not protect against type II cell injury after prolonged exposure to hyperoxia in rats.

van Klaveren R J; Dinsdale D; Pype J L; Demedts M; Nemery B

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American journal of physiology (UNITED STATES) Sep 1997, 273 (3 Pt 1) pL548-55, ISSN 0002-9513 Journal Code: 0370511

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Although the antioxidant properties of N-acetylcysteine (NAC) in vitro are widely accepted, the efficacy of NAC in the prevention of O2 toxicity in vivo is poorly documented. The aim of our study was to investigate the

presumed protective effect of NAC on hyperoxic lung injury, focusing on gamma-glutamyltransferase (gamma-GT) activity and glutathione (GSH) levels in lung tissue, epithelial lining fluid (ELF), and isolated rat type II cells immediately after their isolation and 48 h later when kept in culture in normoxia. Thirty-four male Wistar rats were divided in three groups (n = 10-14) and were exposed to air or to 60 or 85% O₂ for 7 days. One-half of the rats in each group received 200 mg/kg NAC intraperitoneally one time per day from 3 days before exposure until the end of the experiment, and the other one-half received the vehicle. In the 85% O₂-exposed animals, NAC led to more respiratory distress and weight loss. NAC did not prevent the rise in bronchoalveolar lavage lactate dehydrogenase and alkaline phosphatase, but it did prevent the rise in calculated ELF volume. NAC decreased GSH levels (1.4-fold) and gamma-GT activity (1.8-fold) in the air-exposed type II cells. In the 60% O₂-exposed group, no effects of NAC were seen (except for a decrease in gamma-GT mRNA expression), but, in the 85% O₂-exposed group, NAC gave rise to higher GSH (2.6-fold) and higher gamma-GT activity (2.9-fold) in the ELF and lower GSH (6.9-fold) and higher gamma-GT activity (3.6-fold) in the type II cells. Even in culture, GSH levels remained 1.5-fold lower than in the cells from the air-exposed animals and 2-fold lower than in the cells from the 85% O₂-exposed animals. There was increased DNA damage (as assessed by thymidine incorporation) and **apoptosis** after hyperoxia, especially after 60% O₂, and this effect was amplified after NAC **treatment**. Although protective at the endothelial side, NAC **treatment** led to adverse effects at the epithelial side, despite, or probably because of, restoration of the ELF GSH levels in the presence of high O₂ levels. Because NAC is rapidly metabolized to cysteine, it is plausible that the effects of NAC are manifested through the toxic effects of cysteine.

11/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09562288 97471005 PMID: 9326648

The role of polyamine catabolism in polyamine analogue-induced programmed cell death.

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Division of Toxicological Sciences, Department of Environmental Health Sciences, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD 21205, USA.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Oct 14 1997, 94 (21) p11557-62, ISSN 0027-8424 Journal Code: 7505876

Contract/Grant No.: CA57545; CA; NCI; CA63552; CA; NCI; ES07141; ES; NIEHS; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

N1-ethyl-N11-[(cyclopropyl)methyl]-4,8,-diazoundecane (CPENSpm) is a polyamine analogue that represents a new class of antitumor agents that demonstrate phenotype-specific cytotoxic activity. However, the precise mechanism of its selective cytotoxic activity is not known. CPENSpm **treatment** results in the superinduction of the polyamine catabolic enzyme spermidine/spermine N1-acetyltransferase (SSAT) in sensitive cell types and has been demonstrated to induce programmed cell death (PCD). The catalysis of polyamines by the SSAT/polyamine oxidase (PAO) pathway produces H₂O₂ as one product, suggesting that PCD produced by CPENSpm may be, in part, due to oxidative stress as a result of H₂O₂ production. In the sensitive human nonsmall cell line H157, the coaddition of catalase significantly reduces high molecular weight (HMW) DNA (>/=50 kb) and nuclear fragmentation. Important to note, specific inhibition of PAO by N,N'-bis(2, 3-butadienyl)-1,4-butane-diamine results in a significant reduction of the formation of HMW DNA and nuclear fragmentation. In

contrast, the coaddition of catalase or PAO inhibitor has no effect on reducing HMW DNA fragmentation induced by N1-ethyl-N11-[(cycloheptyl)methyl]-4,8,-diazoundecane, which does not induce SSAT and does not deplete intracellular polyamines. These results strongly suggest that H2O2 production by PAO has a role in CPENSpM cytotoxicity in sensitive cells via PCD and demonstrate a potential basis for differential sensitivity to this promising new class of antineoplastic agents. Furthermore, the data suggest a general mechanism by which, under certain stimuli, cells can commit suicide through catabolism of the ubiquitous intracellular polyamines.

11/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09554474 97454333 PMID: 9310408

Effects of chronic lithium **treatment** on ornithine decarboxylase induction and excitotoxic neuropathology in the rat.

Sparapani M; Virgili M; Ortali F; Contestabile A
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Brain research (NETHERLANDS) Aug 8 1997, 765 (1) p164-8,
ISSN 0006-8993 Journal Code: 0045503

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Young adult rats were chronically **treated** with lithium (2.5 mmol/kg/day) for 16 days. The day after the last lithium administration, rats were injected s.c. with the excitotoxic convulsant kainic acid (10 mg/kg). As compared to saline controls, lithium-**treated** rats had no apparent attenuation of convulsions. Furthermore, the induction of brain ornithine decarboxylase and the consequent increase of **putrescine** levels, an index related to the convulsant effects of kainic acid, were similar in saline- and lithium-**treated** rats. Other rats were unilaterally injected with ibotenic acid into the nucleus basalis magnocellularis: no differences were measured in cortical choline acetyltransferase (ChAT) decrease among saline- and lithium-**treated** rats. In both the above experiments, apoptotic cell death was monitored in relevant brain regions of saline- or lithium-**treated** rats through a specific in situ labeling method for fragmented DNA. Whilst morphological evidence for a reduced damage in the olfactory cortex and hippocampus of kainic acid-injected rats was not obtained, lithium-**treated** rats showed a lower decrease of specific neurochemical markers: [3H]D-aspartate uptake and glutamate decarboxylase. This result suggests that mechanisms of recovery, absent in saline-**treated** animals, are elicited by the excitotoxic insult in lithium-**treated** rats.

11/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09523055 97430999 PMID: 9285098

Cellular eukaryotic initiation factor 5A content as a mediator of polyamine effects on growth and **apoptosis**.

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Biological signals (SWITZERLAND) May-Jun 1997, 6 (3) p150-6,

ISSN 1016-0922 Journal Code: 9210083

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The polyamines are essential for eukaryotic cell growth. One of the most critical effects of polyamines on cell growth is the availability of spermidine for the post-translational modification of eIF-5A. Because

hypusine-containing eIF-5A is necessary for cell proliferation, depletion of cellular polyamines suppresses growth by depleting cellular modified eIF-5A content. Excess **putrescine** accumulations in DH23A/b cells induces **apoptosis** and suppresses the formation of hypusine-containing eIF-5A. **Treatment** of DH23A/b cells with diaminoheptane also suppresses modified eIF-5A formation and induces **apoptosis**. These data suggest that suppression of modified eIF-5A formation may play a role in **putrescine**-induced **apoptosis** as well.

11/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09034054 96399630 PMID: 8806101

Effect of suramin on squamous differentiation and **apoptosis** in three human non-small-cell lung cancer cell lines.

Lokshin A; Levitt M L

Department of Medicine, University of Pittsburgh, Pennsylvania, USA.

Journal of cellular biochemistry. Supplement (UNITED STATES) 1996

, 24 p186-97, ISSN 0733-1959 Journal Code: 8207539

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Non-small cell lung cancer (NSCLC) is fatal in approximately 90% of all cases due to the failure of systemic therapy, secondary to resistance to chemotherapy. In such malignancies new therapeutic paradigms are needed. One such approach takes advantage of normal physiologic growth regulatory mechanisms, such as terminal cellular differentiation or **apoptosis**. Suramin, as an antineoplastic drug, has shown efficacy in the **treatment** of prostate cancer and is capable of promoting differentiation in several human cancer cell lines. Little is known about the differentiating effects of suramin in lung cancer. In the present investigation we evaluated the ability of suramin to induce cross-linked envelope (CLE) formation, as a common marker for squamous differentiation and **apoptosis**, in three representative human non-small cell lung cancer cell lines: NCI-H226 (squamous), NCI-H358 (bronchoalveolar [adenocarcinoma]), and NCI-H596 (adenosquamous). Among agents that we have tested, suramin demonstrated the unique ability to induce spontaneous CLE formation in the two cell lines with squamous features, NCI-H226 and NCI-H596. Suramin induced CLE formation was accompanied by DNA fragmentation, a marker for **apoptosis**, in NCI-H596 and NCI-H358, but not in NCI-H226. Stimulation of CLE formation by suramin correlated with the rapid induction of both type II transglutaminase (TG) activity and involucrin expression. These parameters were protein synthesis independent, suggesting posttranslational mechanisms of suramin activity. Induction of differentiation/**apoptosis** markers by suramin did not correlate with its effect on growth. Modulation of signal transduction is a likely candidate mechanism for suramin activity in lung cancer. The relationship between growth, squamous differentiation, and **apoptosis** is considered.

11/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08767154 96114092 PMID: 8845305

Exposure to ornithine results in excessive accumulation of **putrescine** and apoptotic cell death in ornithine decarboxylase overproducing mouse myeloma cells.

Tobias K E; Kahana C

Department of Molecular Genetics and Virology, Weizmann Institute of Science, Rehovot, Israel.

Cell growth & differentiation : the molecular biology journal of the

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Ornithine decarboxylase (ODC) is the first key enzyme in the biosynthesis of polyamines, aliphatic polycations that are indispensable for the process of mammalian cell proliferation. The mouse myeloma cell line, 653-1, massively overproduces ODC due to the amplification of an active ODC gene. The addition of ornithine to the growth medium of 653-1 cells results in a massive increase in the intracellular concentration of **putrescine**, followed by rapid cell death. Ornithine-treated 653-1 cells display fragmented nuclei, chromatin condensation, and an oligonucleosome-sized DNA "ladder"; consequently, their death can be described as **apoptosis**. Accumulation of **putrescine** in 653-1 cells is accompanied by a rapid decrease of protein synthesis activity, suggesting that protein synthesis inhibition may be the cause for the apoptotic death of 653-1 cells. However, since the apoptotic death provoked by exposure of 653-1 cells to ornithine reached a maximal level earlier than that caused by cycloheximide, we conclude that protein synthesis inhibition is unlikely to be the direct cause of the observed apoptotic cell death.

11/3,AB/39 (Item 39 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08727856 96071635 PMID: 7489361

Discovery of betulinic acid as a selective inhibitor of human melanoma that functions by induction of **apoptosis**.

Pisha E; Chai H; Lee I S; Chagwedera T E; Farnsworth N R; Cordell G A; Beecher C W; Fong H H; Kinghorn A D; Brown D M; et al

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago 60612, USA.

Nature medicine (UNITED STATES) Oct 1995, 1 (10) p1046-51,

ISSN 1078-8956 Journal Code: 9502015

Contract/Grant No.: U01 CA 52956; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

As a result of bioassay-guided fractionation, betulinic acid, a pentacyclic triterpene, was identified as a melanoma-specific cytotoxic agent. In follow-up studies conducted with athymic mice carrying human melanomas, tumour growth was completely inhibited without toxicity. As judged by a variety of cellular responses, antitumour activity was mediated by the induction of **apoptosis**. Betulinic acid is inexpensive and available in abundant supply from common natural sources, notably the bark of white birch trees. The compound is currently undergoing preclinical development for the **treatment** or prevention of malignant melanoma.

11/3,AB/40 (Item 40 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08727445 96063665 PMID: 7488168

Is polyamine decrease a common feature of **apoptosis**? Evidence from gamma rays- and heat shock-induced cell death.

Grassilli E; Desiderio M A; Bellesia E; Salomoni P; Benatti F; Franceschi C

Department of Biomedical Sciences, University of Modena, Italy.

Biochemical and biophysical research communications (UNITED STATES) Nov 13 1995, 216 (2) p708-14, ISSN 0006-291X Journal Code: 0372516

Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Here we report that in rat thymocytes undergoing **apoptosis** upon two different stimuli, such as heat shock **treatment** and gamma irradiation, an early mRNA accumulation of ornithine decarboxylase (ODC)--the rate-limiting enzyme of polyamine biosynthesis--was followed by a very marked increase in ODC activity (28-40 and 6-8-fold, respectively). However, polyamine levels started to decrease before the appearance of DNA laddering, being **putrescine** and spermidine strongly diminished (8-12 hs), and spermine even depleted (12 hs). Taken together with our previous data on another model of **apoptosis**, i.e., glucocorticoid-induced cell death (Desiderio et al., Cell Growth Differ. 6: 505-513, 1995), these results suggest that an imbalance of polyamine metabolism, i.e., a strong activation of ODC and a paradoxical decrease of the intracellular polyamine content, might be a general feature of the apoptotic process.

11/3,AB/41 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12914111 BIOSIS NO.: 200100121260

N1-acetylspermidine, polyamine inter-conversion pathway and CNS injury.

AUTHOR: Hatcher J F(a); Rao A M; Dogan A; Dempsey R J

AUTHOR ADDRESS: (a)Univ. of Wisconsin, Madison, WI**USA

JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-7699
2000

MEDIUM: print

CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000

SPONSOR: Society for Neuroscience

ISSN: 0190-5295

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Brain polyamine biosynthesis is altered after CNS injury, the main modifications being significant increases in ornithine decarboxylase (ODC) activity and tissue **putrescine** levels. While ODC is the rate-limiting enzyme in de novo polyamine biosynthesis, it is not solely responsible for **putrescine** formation. We have previously shown that the specific polyamine oxidase (PAO) inhibitor, N1,N4-bis-(2,3-butadienyl)-1,4-butadiamine (MDL 72527) reduced the tissue **putrescine** levels, edema and infarct volume after transient focal cerebral ischemia (MCAO) and traumatic brain injury in rats. In the present study, N1-acetylspermidine accumulation was greater in injured brain regions compared to sham or contralateral regions after inhibiting PAO by MDL 72527. This indicates spermidine/spermine-N1-acetyltransferase (SSAT) activation after CNS injury. At 1-day after CNS injury, **putrescine** accumulates while ODC activity declines to near basal levels. Secondly, the increase in N1-acetylspermidine levels at 1-day after CNS trauma paralleled the decrease in **putrescine** after **treatment** with MDL 72527. This suggests that the increase in **putrescine** at 1-day after CNS injury is mediated by the SSAT/PAO pathway, consistent with increased SSAT mRNA after transient ischemia. Our data also indicate that the **putrescine** is largely formed by PAO action on N1-acetylspermidine, and the contribution of PAO direct oxidation of spermidine to **putrescine** appears to be negligible. The neuroprotective effects of MDL 72527, besides reducing the **putrescine** formation, may be due in part to attenuation of the toxic by-products 3-acetamidopropanal and hydrogen peroxide, which may induce **apoptosis** after CNS injury.

11/3,AB/42 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

11779520 BIOSIS NO.: 199900025629

alpha-Difluoromethylornithine inhibits N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in zinc-deficient rats: Effects on esophageal cell proliferation and **apoptosis**.

AUTHOR: Fong Louise Y Y(a); Pegg Anthony E; Magee Peter N

AUTHOR ADDRESS: (a)Dep. Microbiol. and Immunol., Kimmel Cancer Inst., Thomas Jefferson Univ., 1020 Locust St., Phil**USA

JOURNAL: Cancer Research 58 (23):p5380-5388 Dec. 1, 1998

ISSN: 0008-5472

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Sustained, increased cell proliferation induced by dietary zinc deficiency in rats plays a critical role in esophageal carcinogenesis. It is the determining factor that converts an otherwise nontumorigenic dose of N-nitrosomethylbenzylamine (NMBA) into a highly tumorigenic one. We studied whether the increased esophageal cell proliferation and susceptibility to NMBA-induced carcinogenesis induced by zinc deficiency can be inhibited by alpha-difluoromethylornithine (DFMO), an enzyme-activated, irreversible inhibitor of ornithine decarboxylase (the first enzyme in polyamine synthesis). Weanling rats were divided into four groups: Zn+/ DFMO-, Zn+/DFMO+, Zn-/DFMO-, and Zn-/DFMO+. They were fed ad libitum either a zinc-sufficient (Zn+, 75 ppm zinc) or a zinc-deficient (Zn-, 4 ppm zinc) diet and given either deionized water (DFMO-) or 1% DFMO in deionized water (DFMO+). After 5 weeks, 5-19 animals from each group were sacrificed after in vivo 5-bromo-2'-deoxyuridine labeling to detect cells in S phase. The remaining animals in each group were given a single intragastric dose of NMBA at 2 mg/kg and sacrificed 12 weeks later for tumor incidence analysis. At week 5, DFMO **treatment** greatly decreased (by 48-82%) the levels of **putrescine** and spermidine in rat esophagus, colon, and liver, irrespective of dietary zinc intake. The increased esophageal cell proliferation induced by dietary zinc deficiency, as measured by the labeling index, the number of labeled cells, and the total number of cells, was substantially reduced by DFMO. This was accompanied by an increase in the rate of **apoptosis**. In addition, the expression of bax protein, an **apoptosis** accelerator, was markedly stronger in esophagi from Zn-/DFMO+ animals that showed increased **apoptosis**, whereas increased expression of bcl-2, an inhibitor of **apoptosis**, was only seen in the highly proliferative, zinc-deficient esophagus (Zn-/DFMO-). At week 12 after NMBA dosing, DFMO reduced the incidence of esophageal tumors from 80 to 4% in zinc-deficient rats. Our data showed that DFMO effectively inhibited the increased esophageal cell proliferation induced by dietary zinc deficiency and reduced the incidence of esophageal tumors induced by a single dose of NMBA in zinc-deficient animals. Our results also indicate a role for increased **apoptosis** in the mechanism(s) whereby DFMO brings about the inhibition of cell, proliferation and tumor induction. These findings support a role for DFMO as a chemopreventive agent.

1998

11/3,AB/43 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

11449647 BIOSIS NO.: 199800230979

Polyamines regulate expression of the neoplastic phenotype in mouse skin.

AUTHOR: Soler Alejandro Peralta; Gilliard Gwendolyn; Megosh Louis; George Kenneth; O'Brien Thomas G(a)

AUTHOR ADDRESS: (a)Lankenau Med. Res. Cent., 1001 Lancaster Ave.,
Wynnewood, PA 19096**USA

JOURNAL: Cancer Research 58 (8):p1654-1659 April 15, 1998

ISSN: 0008-5472

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Elevated polyamine levels are characteristic of many types of neoplastic cells and tissues. We demonstrate that in transgenic mice overexpressing ornithine decarboxylase in skin, changes in tissue polyamine levels, particularly **putrescine**, control the development and maintenance of the neoplastic phenotype. A specific inhibitor of the transgene, alpha-difluoromethylornithine (DFMO), reversibly blocked the appearance of squamous papillomas after carcinogen **treatment**. Furthermore, **treatment** of papilloma-bearing mice with DFMO caused rapid tumor regression, also in a reversible manner. Although the rate of **apoptosis** in papillomas was unaffected by acute DFMO **treatment**, tumor cell proliferation was rapidly decreased after drug **treatment**. Conversely, proliferation of normal epidermal keratinocytes was unaffected by DFMO **treatment**. The regulatory polyamine in this model appears to be **putrescine**, the immediate product of ornithine decarboxylase. These results demonstrate that elevated polyamine levels are required for both the development and maintenance of the neoplastic phenotype in skin.

1998

11/3,AB/44 (Item 4 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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11320268 BIOSIS NO.: 199800101600

Direct inhibitory effect of uremic toxins and polyamines on proliferation of VERO culture cells.

AUTHOR: Stabellini Giordano(a); Mariani Giustiniano; Pezzetti Furio(a); Calastrini Carla(a)

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Universita di Ferrara, 44100 Ferrara**Italy

JOURNAL: Experimental and Molecular Pathology 64 (3):p147-155 1997

ISSN: 0014-4800

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The dialysate fluid of uremic patients exhibits, in vitro, an inhibitory effect on cell growth, owing to urea, guanidino compounds, and substances named middle molecules. The polyamines are compounds which exhibit high levels in biological fluids during either normal development or disease such as psoriasis, uremia, and tumors. Dialysate and middle molecules show toxicity and degeneration of the organotype cultures, whereas the free polyamines and nonrecirculated dialysate do not have any toxic effect. The aim of this study is to analyze the effects of polyamines, nonrecirculated dialysate, and middle molecules of uremic patients in periodic hemodialysis on cultured VERO (fibroblast-like cells) growth. These cells show an inhibition of growth in middle molecules or 2×10^{-4} M **putrescine** and a stimulation with nonrecirculated dialysate and 2×10^{-8} M **putrescine**. The effect is

different because the cultures with middle molecules begin growth again after 24 hr, whereas in the presence of 2×10^{-4} M **putrescine** no further growth is observed. Cells maintained in middle molecules + 2×10^{-8} M **putrescine** show an irreversible degeneration, attesting a toxic effect due to the low molarities of **putrescine**. The electron microscopy shows alteration of cytoplasmic, mitochondrial, and nuclear membranes, but no chromatin fragmentation with either middle molecules or 2×10^{-4} M **putrescine**: this suggests that the cells do not die of **apoptosis**. In conclusion, during uremia the polyamines could cause toxic effects, even at low concentrations, on cells stressed by other toxic stimuli.

1997

11/3,AB/45 (Item 5 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)
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10574325 BIOSIS NO.: 199699195470

Inhibitory role of polyamines in dexamethasone-induced **apoptosis** of mouse thymocytes.

AUTHOR: Choi Sang-Hyun; Kim Yong-Hoon; Hong Gi-Hyun; Shin Kyung-Ho; Chun Yeon-Sook; Chun Boe-Gwun(a)

AUTHOR ADDRESS: (a)Dep. Pharmacol., Korea Univ. Coll. Med., Seoul 136-705**
South Korea

JOURNAL: Korean Journal of Pharmacology 32 (1):p113-123 1996

ISSN: 0377-9459

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English; Korean

ABSTRACT: It has been well known that polyamines ensure the stability of chromatin structure and the fidelity of DNA transcription. This study was carried out to evaluate the effect of polyamines on the **apoptosis** of mouse thymocytes induced by dexamethasone and polyamine synthesis inhibitors. 1) In the histological death findings of thymocytes double-stained with acridine orange and ethidium bromide, the apoptotic and the necrotic fractions (AF; NF) in the control group were $9.4 \pm 4.2\%$ and $4.5 \pm 5.3\%$, respectively. Dexamethasone (3 times 10^{-8} M: DX) increased AF upto $52.0 \pm 8.1\%$ and did not change NF, but A23187 (5 times 10^{-7} M: A2) increased AF and NF upto $45.0 \pm 8.9\%$ and $20.5 \pm 10.6\%$, respectively. 2) The thymocyte viability was significantly reduced by DX, DHEA (1 times 10^{-4} M), A2, DFMO (1 times 10^{-4} M), and MGBG (1 times 10^{-4} M), respectively. It was, however, little affected by aminoguanidine (1 times 10^{-4} M: AG), **putrescine** (1 times 10^{-5} M: PT), spermidine (1 times 10^{-3} M: SD), and spermine (1 times 10^{-5} M: SM). 3) The genomic DNA of mouse thymocyte was markedly fragmented by DX and A2, respectively, and to a lesser extent, by DHEA, but was little affected by MGBG, DFMO, AG, and each of polyamines. 4) The DX induced reduction of thymocyte viability was moderately attenuated by DHEA, but little affected by DFMO, MGBG, and AG. However, SM significantly attenuated the viability reduction induced by A2 as well as DX. 5) The thymocyte viability reduction by MGBG and DFMO was significantly attenuated by only SM among three polyamines applied in this study. 6) The thymocyte viability reduction by combined **treatments** of DX with DFMO and MGBG, respectively, was significantly attenuated by SM, and moderately by PT. But the viability reduction by combined **treatment** of DX with AG or DHEA was not affected by polyamines. These results suggest that polyamines, particularly spermine, might play the inhibitory role in thymocyte **apoptosis** and the inhibitory effect can be ascribed in part to the increase of polyamine uptake by thymocytes pretreated with DFMO and MGBG.

1996

11/3,AB/46 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
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10311705 BIOSIS NO.: 199698766623
Interaction between reactive oxygen radicals (ROS) and polyamine metabolism
in monocrotaline-treated pulmonary artery endothelial cells (PAEC).
AUTHOR: Aziz S M; Toborek M; Hennig B; Gellin G; Endean R
AUTHOR ADDRESS: Univ. Kentucky, Lexington, KY 40536-0082**USA
JOURNAL: FASEB Journal 10 (3):pA584 1996
CONFERENCE/MEETING: Experimental Biology 96, Part II Washington, D.C., USA
April 14-17, 1996
ISSN: 0892-6638
RECORD TYPE: Citation
LANGUAGE: English
1996

11/3,AB/47 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2002 Elsevier Science B.V. All rts. reserv.

10990441 EMBASE No: 2001035077
Effects of alpha-difluoromethylornithine on the Fas expression and
apoptosis in Hep-2 cells
Alvarez M.G.; Marty C.; Mori G.; Rivarola V.
Dr. V. Rivarola, Dpto. Biologia Molecular, Facultad de Ciencias Exactas,
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Biocell (BIOCELL) (Argentina) 2000, 24/3 (213-216)
CODEN: BOCEE ISSN: 0327-9545
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 13

DFMO is an irreversible inhibitor of ornithine decarboxylase (ODC), the
key enzyme in mammalian polyamine biosynthesis, and has been shown to
induce **apoptosis**. In this paper, the relation between the effects of
DFMO on the polyamine content, apoptotic index and Fas expression in HEP-2
cells was determined. Fas is a type I membrane protein with a molecular
mass of 45 kDa, which mediates **apoptosis**. The results suggest that
the **treatment** with the polyamine inhibitor DFMO induced the
expression of the surface antigen Fas, which could be responsible for
trigger **apoptosis** in these cells.

11/3,AB/48 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE
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10977763 EMBASE No: 2001021302
Apoptosis induced by lprime-acetoxychavicol acetate in Ehrlich
ascites tumor cells is associated with modulation of polyamine metabolism
and caspase-3 activation
Moffatt J.; Hashimoto M.; Kojima A.; Kennedy D.O.; Murakami A.; Koshimizu
K.; Ohigashi H.; Matsui-Yuasa I.
I. Matsui-Yuasa, Department of Food and Nutrition, Faculty of Human Life
Sciences, Osaka City University, Osaka 558-8585 Japan
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Carcinogenesis (CARCINOGENESIS) (United Kingdom) 2000, 21/12
(2151-2157)
CODEN: CRNGD ISSN: 0143-3334
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 50

The efficacy of the antitumor activity of lprime-acetoxychavicol acetate (ACA), reported to be a suppressor of chemically induced carcinogenesis, was evaluated in Ehrlich ascites tumor cells. ACA **treatment** resulted in changes in morphology and a dose-dependent suppression of cell viability. **Apoptosis**, characterized by nuclear condensation, membrane blebbing, cell shrinkage and a significant induction of caspase-3-like protease activity at 8 h in a time-course study were observed. Formation of apoptotic bodies was preceded by lowering of intracellular polyamines, particularly **putrescine**, and both dose- and time-dependent inhibitory and activation effect by ACA on ornithine decarboxylase (ODC) and spermidine/spermine NSUPl-acetyl-transferase (SSAT), respectively. Administration of exogenous polyamines prevented. ACA-induced **apoptosis** represented by a reduction in the number of apoptotic bodies and also caused reduction in the induced caspase-3-like protease activity at 8 h. These findings suggest that the anticarcinogenic effects of ACA might be partly due to perturbation of the polyamine metabolic pathway and triggering of caspase-3-like activity, which result in **apoptosis**.

11/3,AB/49 (Item 3 from file: 72)
DIALOG(R)File 72:EMBASE
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07692781 EMBASE No: 1999179808

Polyamine-fas interactions: Inhibition of polyamine biosynthesis in MRL-lpr/lpr mice is associated with the up-regulation of fas mRNA in thymocytes

Hui-Chen H.; Thomas T.; Sigal L.H.; Thomas T.J.
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AUTHOR EMAIL: thomastj@UMDNJ.edu
Autoimmunity (AUTOIMMUNITY) (United Kingdom) 1999, 29/4 (299-309)
CODEN: AUIME ISSN: 0891-6934
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 53

MRL-lpr/lpr is a strain of mice that develops spontaneous signs of the autoimmune disease, systemic lupus erythematosus (SLE or lupus). The lpr (lymphoproliferation) defect has been identified as an insertion of an early transposon (ETn) derived sequence into the fas **apoptosis** gene. We studied the in vitro effects of difluoromethylornithine (DFMO), an irreversible inhibitor of the polyamine biosynthetic enzyme, ornithine decarboxylase (ODC), on the expression of fas in MRL-lpr/lpr mice as well as in congenic MRL-+/+ and autoimmune NZB/W strains. Using Northern blot hybridization and reverse transcription polymerase chain reaction (RT-PCR), we found that DFMO **treatment** resulted in an increase in the expression of fas mRNA in the thymus of MRL-lpr/lpr mice. Using RT-PCR, we further found that the increased expression of fas was associated with the suppression of chimeric ETn/fas mRNA. With fractionated CD4sup + and CD8sup + T cells, we found a cell-specific effect of DFMO on chimeric ETn/fas expression in CD8sup + cells. ETn/fas expression was detected in CD8sup + T cells from untreated mice, but it was eliminated after DEMO **treatment**. HPLC analysis of polyamines showed depletion of **putrescine** and partial reduction of spermidine (35%) in DFMO-**treated** mice compared to controls. These results indicate that DFMO-mediated polyamine depletion

is linked to the regulation of fas and chimeric ETn/fas in MRL-lpr/lpr mice. Elevated levels of polyamines in this strain, as found in earlier studies, may be associated with the progression of the autoimmune disease by altering the expression of fas gene or by facilitating the expression of chimeric ETn/fas. Our data also provide new mechanistic insights into the beneficial effects of DFMO on these mice.

? s s1 and (administer? (w) putrescin?)
19864 S1
652293 ADMINISTER?
19852 PUTRESCIN?
22 ADMINISTER? (W) PUTRESCIN?
S14 22 S1 AND (ADMINISTER? (W) PUTRESCIN?)

? rd

>>>Duplicate detection is not supported for File 304.

>>>Records from unsupported files will be retained in the RD set.

...completed examining records

S15 8 RD (unique items)

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>>>No matching display code(s) found in file(s): 304

15/3,AB/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

11119906 21124803 PMID: 11223867

Effects of polyamines on DNA synthesis using various subcellular DNA polymerases extracted from normal rat liver, tumour-bearing rat liver, and tumour cells.

Taguchi T; Kurata S; Ohashi M

Department of Gene Regulation and Protein Function, Tokyo Metropolitan Institute of Gerontology, Japan. ttaguchi@tmig.or.jp

Cell biochemistry and function (England) Mar 2001, 19 (1) p19-26,

ISSN 0263-6484 Journal Code: 8305874

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The effects of polyamines on DNA synthesis in vitro using various subcellular DNA polymerase fractions from normal and tumour-bearing rat livers, and tumour cells were investigated. When nuclear and mitochondrial DNA polymerase fractions were used, DNA synthesis on activated DNA was increased 3.5-8-fold by the addition of 20 mM **putrescine** or cadaverine. However, DNA synthesis was not stimulated by the addition of spermidine or spermine at any concentration tested. In contrast, DNA synthesis using the cytoplasmic DNA polymerase fraction was not stimulated at various concentrations of any of the four polyamines tested. The stimulatory effects of **putrescine** and cadaverine were absent when nuclear fractions from tumour-bearing rat liver or from tumour cells were used. In addition, in vitro DNA synthesis was not stimulated by 20 mM **putrescine** or cadaverine when nuclear extracts from the livers of rats **administered putrescine** subcutaneously were used. The specific activities of DNA polymerases extracted from tumour cells and tumour-bearing rat liver were already fully stimulated. These results suggest that DNA polymerases in tumour cells and tumour-bearing liver cells are stimulated by trapped **putrescine** produced in tumour cells and are thus no longer activated by exogenous **putrescine**.

15/3,AB/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10977402 20534479 PMID: 11083508

Effects of felbamate on brain polyamine changes following transient cerebral ischemia in the Mongolian gerbil.

Bramanti P; Arcadi F A; Di Bella P; Sessa E; D'Aleo G; Trimarchi G R

Centro per lo Studio ed il Trattamento dei Neurolesi Lungodegenti, Chair of Neurophysiopathology, School of Medicine, University of Messina, Italy.

Acta neurologica Scandinavica (DENMARK) Nov 2000, 102 (5) p309-16,

ISSN 0001-6314 Journal Code: 0370336

Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We sought to determine whether treatment with felbamate was capable to reduce the accumulation of **putrescine** induced by transient forebrain ischemia in the Mongolian gerbil. Gerbils underwent 10 min ligation of common carotid arteries followed by recirculation. Immediately after the release of the arterial occlusion, felbamate (75 and 150 mg kg(-1) i.p.) was administered. **Putrescine** and polyamine levels were measured in hippocampus and striatum at 1, 8, 24 and 48 h after recirculation. **Putrescine** levels appeared enhanced already 8 h after the release of the arterial occlusion and kept increasing up to 48 h in the hippocampus and striatum. No significant changes in spermidine levels during recirculation were detected. Conversely, spermine appeared to decrease in the hippocampus while it did not show changes in the striatum. Felbamate significantly reduced the ischemia induced changes in **putrescine** brain content only at the dose of 150 mg kg(-1) i.p.

15/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08390117 95157842 PMID: 7854616

On the neurotoxicity of systemically administered **putrescine**: influence of kinetic factors.

Camon L; de Vera N; Martinez E
Department of Pharmacology and Toxicology, Consejo Superior de Investigaciones Cientificas (CSIC), Barcelona, Spain.
Neurotoxicology (UNITED STATES) Fall 1994, 15 (3) p759-63, ISSN 0161-813X Journal Code: 7905589

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Putrescine (PUT) given ip to male rats produced a dose-dependent behavioural response. The observed signs were mainly shaking behaviour and motor disorders. The severity of the motor signs closely correlated with cortical PUT levels. After [14C]-PUT, the levels of related radioactivity ([14C]-PUTrr) in frontal cortex paralleled the levels of tracer in blood. Furthermore, the levels of tracer in blood and in frontal cortex were higher in the animals with toxicity signs than in non-affected ones. The frontal cortex levels of polyamines determined by HPLC revealed that only PUT paralleled the severity of the clinical status of the rats. No modifications of spermidine (SD) or spermine (SM) content were detected. Two hours after [14C]-PUT administration, only about 30% of the cortical [14C]-PUTrr was analyzed as PUT itself and no radioactivity was detected as SD and SM. Our results suggest that the radioactivity not associated to PUT could be related to more polar metabolites than SD or SM as acetylated derivatives.

15/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06748667 91060008 PMID: 1983813

Putrescine is involved in the vitamin D action in chick intestine.
Shinki T; Tanaka H; Takito J; Yamaguchi A; Nakamura Y; Yoshiki S; Suda T
Department of Biochemistry, School of Dentistry, Showa University, Tokyo, Japan.

Gastroenterology (UNITED STATES) Jan 1991, 100 (1) p113-22, ISSN 0016-5085 Journal Code: 0374630

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We have reported that a single injection of 1 alpha,25-dihydroxyvitamin D3 into vitamin D-deficient chicks produces a marked increase of **putrescine** accumulation in the duodenum from two different sources, ornithine and spermidine. In the present study, the effects of **putrescine** depletion and its supplementation on duodenal villus length and calcium absorption were examined in newborn and 5-week-old chicks. Administering either alpha-difluoromethylornithine, a specific inhibitor of ornithine decarboxylase, or N1,N4-bis(2,3-butadienyl)-1,4-butanediamine, a specific inhibitor of polyamine oxidase, to newborn chicks significantly decreased the duodenal content of **putrescine** and calcium transport activity. The **putrescine** depletion also induced shortening of the duodenal villus length. The inhibition of calcium absorption and villus length in the **putrescine**-depleted chicks was almost completely restored by **administering putrescine** to the birds. The effect of the **putrescine** depletion and its supplementation on the duodenal villus length and the calcium absorption was reproduced in 5-week-old vitamin D-deficient chicks given vitamin D3 or 1 alpha,25-dihydroxyvitamin D3. These results clearly indicate that **putrescine** is somehow involved in the vitamin D action in maintaining the morphological and functional development of the intestinal villus mucosa.

15/3,AB/5 (Item 5 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

04850183 85233519 PMID: 3924844

Antitumor effects of two polyamine antimetabolites combined with mitomycin C on human stomach cancer cells xenotransplanted into nude mice.

Fujimoto S; Igarashi K; Shrestha R D; Miyazaki M; Okui K

International journal of cancer. Journal international du cancer (UNITED STATES) Jun 15 1985, 35 (6) p821-5, ISSN 0020-7136 Journal Code: 0042124

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The antitumor effects of alpha-difluoromethylornithine (DFMO), methylglyoxal-bis-guanyldrazone (MGBG) and mitomycin C (MMC), administered separately or in various combinations, on human stomach cancer cells xenotransplanted into BALB/c nude mice were studied using the protocol of Battelle's Columbus Laboratories (Ovejera et al., 1978). DFMO (1,000 mg/kg in 2 divided doses) and MGBG (50 mg/kg) were given intraperitoneally (i.p.) for 7 consecutive days from the time when the tumor weighed about 100 mg. MMC (2 mg/kg) was given i.p. every other day from the same time. Animals treated with either DFMO or MGBG alone displayed tumor growth comparable to that seen in untreated controls. In mice treated with DFMO plus MGBG with or without MMC, or in mice treated only with MMC, tumor growth was significantly lower than in untreated mice. In the group which received only combined DFMO/MGBG there was a rapid regrowth of the tumor after termination of therapy. Tumor **putrescine** levels decreased within 4 days following the administration of DFMO; however, spermidine levels did not decline with either DFMO or MGBG treatment even after 7 days. When combined DFMO/MGBG was given, there was a significant decline in spermidine levels 7 days after the initiation of treatment. In contrast, when MMC alone was **administered**, **putrescine** and spermidine levels in the tumor did not differ from those in control mice. Spermine decreased markedly in tumor with the combined administration of DFMO/MGBG as well as with combined DFMO/MGBG/MMC, but decreased only slightly when MMC alone or MMC plus either DFMO or MGBG was administered. By the 7th treatment day, DNA biosynthesis in the tumor had dropped markedly in all groups except those receiving DFMO or MGBG alone.

15/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04024785 83014639 PMID: 6812032

Copenhagen rat prostatic tumor ornithine decarboxylase activity (ODC) and the effect of the ODC inhibitor alpha-difluoromethylornithine.

Heston W D; Kadmon D; Lazan D W; Fair W R

Prostate (UNITED STATES) 1982, 3 (4) p383-9, ISSN 0270-4137
Journal Code: 8101368

Contract/Grant No.: CA23665; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The R3327MAT-Lu tumor is a rapidly growing anaplastic derivative of the Dunning R3327 prostatic adenocarcinoma. We have found the ornithine decarboxylase (ODC) activity of this tumor to be as sensitive to inhibition by alpha-difluoromethylornithine (DFMO) as normal rat prostate. The same was true for all the other R3327 tumor derivatives we studied. The in vivo inhibition of ODC by DFMO allowed increased uptake of exogenously **administered putrescine** by the R3327AT tumor. Further, DFMO was inhibitory to the growth of the R3327MAT-Lu both in vitro and in vivo.

15/3,AB/7 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09149648 BIOSIS NO.: 199497158018

On the neurotoxicity of systemically **administered putrescine**:

Influence of kinetic and metabolic factors.

AUTHOR: Camon Lluisa; De Vera Nuria; Martinez Emili

AUTHOR ADDRESS: Dep. Pharmacol. Toxicol., C.S.I.C., Barcelona**Spain

JOURNAL: Neurotoxicology (Little Rock) 14 (4):p556 1993

CONFERENCE/MEETING: Fourth Meeting of the International Neurotoxicology Association Helsingor, Denmark June 6-11, 1993

ISSN: 0161-813X

RECORD TYPE: Citation

LANGUAGE: English

1993

15/3,AB/8 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

03973205 BIOSIS NO.: 000076058771

COPENHAGEN RAT PROSTATIC TUMOR ORNITHINE DECARBOXYLASE ACTIVITY AND THE EFFECT OF THE ORNITHINE DECARBOXYLASE INHIBITOR ALPHA DI FLUOROMETHYL ORNITHINE

AUTHOR: HESTON W D W; KADMON D; LAZAN D W; FAIR W R

AUTHOR ADDRESS: WASH. UNIV. SCH. MED., DIV. UROL., ST. LOUIS, MO. 63110.

JOURNAL: PROSTATE 3 (4). 1982 (RECD. 1983). 383-390. 1982

FULL JOURNAL NAME: Prostate

CODEN: PRSTD

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: The R3327MAT-Lu tumor is a rapidly growing anaplastic derivative of the Dunning R3327 prostatic adenocarcinoma. The ornithine decarboxylase (ODC) activity of this tumor is as sensitive to inhibition by .alpha.-difluoromethylornithine (DFMO) as normal rat prostate. The

same was true for all the other R3327 tumor derivatives studied. The in vivo inhibition of ODC by DFMO allowed increased uptake of exogenously administered putrescine by the R3327AT tumor. DFMO was inhibitory to the growth of the R3327MAT-Lu both in vitro and in vivo.

1982

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>>>No matching display code(s) found in file(s): 304

21/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13620792 22209316 PMID: 12220664

Caspase activation in etoposide-treated fibroblasts is correlated to ERK phosphorylation and both events are blocked by polyamine depletion.

Stefanelli Claudio; Tantini Benedetta; Fattori Monia; Stanic' Ivana; Pignatti Carla; Clo Carlo; Guarnieri Carlo; Calderera Claudio M; Mackintosh Caroline A; Pegg Anthony E; Flamigni Flavio

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FEBS letters (Netherlands) Sep 11 2002, 527 (1-3) p223-28, ISSN 0014-5793 Journal Code: 0155157

Contract/Grant No.: CA-18138; CA; NCI; GN-2629; PHS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Activation of the extracellular signal-regulated kinases (ERKs) 1 and 2 is correlated to cell survival, but in some cases ERKs can act in signal transduction pathways leading to **apoptosis**. Treatment of mouse fibroblasts with 20 microM etoposide elicited a sustained phosphorylation of ERK 1/2, that increased until 24 h from the treatment in parallel with caspase activity. The inhibitor of ERK activation PD98059 abolished caspase activation, but caspase inhibition did not reduce ERK 1/2 phosphorylation, suggesting that ERK activation is placed upstream of caspases. Both ERK and caspase activation were blocked in cells depleted of polyamines by the ornithine decarboxylase inhibitor alpha-difluoromethylornithine (DFMO). In etoposide-treated cells, DFMO also abolished phosphorylation of c-Jun NH(2)-terminal kinases triggered by the drug. Polyamine replenishment with exogenous putrescine restored the ability of the cells to undergo caspase activation and ERK 1/2 phosphorylation in response to etoposide. Ornithine decarboxylase activity decreased after etoposide, indicating that DFMO exerts its effect by depleting cellular polyamines before induction of **apoptosis**. These results reveal a role for polyamines in the transduction of the death signal triggered by etoposide.

21/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13526425 22090931 PMID: 12095537

Growth, morphological and biochemical changes in oxa-spermine derivative-treated MCF-7 human breast cancer cells.

Pavlov V; Rodilla V; Kong Thoo Lin P

Department of Human and Animal Physiology, Faculty of Biology, University of Sofia St. Kliment Ohridski, Dr. Tzankov Blvd. 8, 1164 Sofia, Bulgaria. vpavlov@biofac.uni-sofia.bg

Life sciences (England) Jul 26 2002, 71 (10) p1161-73, ISSN 0024-3205 Journal Code: 0375521

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The growth inhibitory properties of two oxa-spermine derivatives named compound 1 and compound 2, representatives of a novel type of polyamine derivatives, were studied. Dose-response growth inhibitory curves obtained after 48h drug exposure demonstrated the much higher cytotoxic activity of compound 1 towards MCF-7 human breast cancer cells. Further experiments with compound 1 showed that this oxa-spermine derivative exhibited

considerable cytotoxicity with IC(50) values of 3.74 microM and 2.93 microM after 24h and 48h drug exposure respectively. In MCF-7 cells, after 8h drug (10 microM) exposure it caused shrinkage, chromatin condensation and nuclear fragmentation. However, no clear DNA laddering was detected in treated cells. Drug treatment provoked an increase in polyamine oxidase (PAO) activity. This enzyme is able to produce cytotoxic H(2)O(2) and 3-acetamidopropanal, catalyzing the oxidative deamination of N(1)-acetylated derivatives of spermine and spermidine to spermidine and **putrescine** respectively. Taken together these data demonstrate that the novel oxa-polyamine derivative compound 1 has considerable cytotoxic activity towards MCF-7 cells and indicate that an induction of PAO may be involved in its cytotoxic and apoptotic effects.

21/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13520095 22189900 PMID: 12201060

p53-independent **apoptosis** in UV-irradiated mouse skin: possible inhibition by 50 Hz magnetic fields.

Kumlin Timo; Heikkinen Paivi; Kosma Veli-Matti; Alhonen Leena; Janne Juhani; Juutilainen Jukka

Department of Environmental Sciences, University of Kuopio, P.O. Box 1627, 70211 Kuopio, Finland. timo.kumlin@uku.fi

Radiation and environmental biophysics (Germany) Jun 2002, 41 (2) p155-8, ISSN 0301-634X Journal Code: 0415677

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Our recent results suggest that 50 Hz magnetic fields (MF) enhance ultraviolet (UV)-induced tumorigenesis in mouse skin. The aim of the present experiment was to study suppression of **apoptosis** as a possible mechanism for MF effects on skin tumorigenesis. Another aim was to test the importance of a UV and MF exposure schedule, particularly the role of MF exposure prior to UV irradiation. Female mice were exposed to a UV dose of 2 human MED and to 100 microT MF of 50 Hz, using the following exposure schedules: group 1 sham MF 24 h, UV 1 h, sham MF 24 h; group 2 sham MF 24 h, UV 1 h, MF 24 h; group 3 MF 24 h, UV 1 h, MF 24 h. Lamps emitting simulated solar radiation (SSR) were used for UV irradiation. Skin samples were analysed for **apoptosis**, expression of the p53 gene, activity of the enzyme ornithine decarboxylase (ODC) and polyamine concentrations. A significantly ($p = 0.017$) lower number of apoptotic cells was measured in group 2 compared to group 1. A similar but not statistically significant ($p = 0.064$) decrease was also detected in group 3. No p53 expression was detected in any sample. The levels of ODC and **putrescine** did not differ significantly between the UV-only and UV and MF-exposed groups. Spermidine and spermine levels were significantly ($p = 0.014$ and 0.014 , respectively) lower in group 3 than in group 1, but no decrease was observed in group 2. Our findings suggest that SSR induces p53-independent **apoptosis** in mouse skin and that the apoptotic response may be inhibited by exposure to MF. The exposure schedule did not alter the MF effect. The results do not support a causal role for polyamines in MF effects on **apoptosis**.

21/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13418906 21847967 PMID: 11859413

Transglutaminase activity during senescence and programmed cell death in the corolla of tobacco (Nicotiana tabacum) flowers.

Serafini-Fracassini D; Del Duca S; Monti F; Poli F; Sacchetti G; Bregoli A M; Biondi S; Della Mea M

Dipartimento di Biologia Evoluzionistica Sperimentale, Università di
Bologna, Bologna, Italy.

Cell death and differentiation (England) Mar 2002, 9 (3) p309-21,
ISSN 1350-9047 Journal Code: 9437445

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Corolla life span of undetached flowers of *Nicotiana tabacum* was divided into stages from the closed corolla (stage 1) through anthesis (stage 5) to death (stage 9). Senescence began around stage 6 in the proximal part, concomitantly with DNA laddering. Nuclear blebbing, DNA laddering, cell wall modification, decline in protein, water, pigment content and membrane integrity were observed during senescence and PCD. Transglutaminase activity was measured as mono- and bis-derivatives of **putrescine** (mono-PU; bis-PU) and bis-derivatives of spermidine (bis-SD). Bis-derivatives decreased with the progression of senescence, while mono-PU increased during early senescence; derivatives were present in different amounts in the proximal and distal parts of the corolla. In excised flowers, exogenous spermine delayed senescence and PCD, and caused an increase in free and acid-soluble conjugated PA levels. Bis-PU was the most abundant PA-derivative before DNA laddering stage; thereafter, bis-PU generally decreased and mono-PU became the most abundant derivative.

21/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13248821 21981868 PMID: 11986788

Cell cycle phase perturbations and **apoptosis** in tumour cells induced by aplidine.

Erba E; Bassano L; Di Liberti G; Muradore I; Chiorino G; Ubezio P; Vignati S; Codegoni A; Desiderio M A; Faircloth G; Jimeno J; D'Incalci M

Cancer Pharmacology Laboratory, Department of Oncology, Istituto di Ricerche Farmacologiche Mario Negri, via Eritrea 62, 20157 Milan, Italy.
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British journal of cancer (Scotland) May 6 2002, 86 (9) p1510-7,
ISSN 0007-0920 Journal Code: 0370635

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Aplidine, dehydrididemnin B, is a marine depsipeptide isolated from the Mediterranean tunicate *Aplidium albicans* currently in phase II clinical trial. In human Molt-4 leukaemia cells Aplidine was found to be cytotoxic at nanomolar concentrations and to induce both a G(1) arrest and a G(2) blockade. The drug-induced cell cycle perturbations and subsequent cell death do not appear to be related to macromolecular synthesis (protein, RNA, DNA) since the effects occur at concentrations (e.g. 10 nM) in which macromolecule synthesis was not markedly affected. Ten nM Aplidine for 1 h inhibited ornithine decarboxylase activity, with a subsequently strong decrease in **putrescine** levels. This finding has questionable relevance since addition of **putrescine** did not significantly reduce the cell cycle perturbations or the cytotoxicity of Aplidine. The cell cycle perturbations caused by Aplidine were also not due to an effect on the cyclin-dependent kinases. Although the mechanism of action of Aplidine is still unclear, the cell cycle phase perturbations and the rapid induction of **apoptosis** in Molt-4 cells appear to be due to a mechanism different from that of known anticancer drugs. Copyright 2002 Cancer Research UK

21/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13235203 22017168 PMID: 12022477

Biochemical effects and growth inhibition in MCF-7 cells caused by novel sulphonamido oxa-polyamine derivatives.

Pavlov V; Lin P Kong Thoo; Rodilla V

Department of Human and Animal Physiology, Faculty of Biology, University of Sofia St. Kliment Ohridski, Bulgaria.

Cellular and molecular life sciences : CMLS (Switzerland) Apr 2002, 59

(4) p715-23, ISSN 1420-682X Journal Code: 9705402

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The novel polyamine derivatives sulphonamido oxa-spermine (oxa-Spm) and sulphonamido oxa-spermidine (oxa-Spd) exhibited rapid cytotoxic action towards MCF-7 human breast cancer cells with IC50 values of 4.35 and 6.47 pM, respectively, after 24-h drug exposure. Neither compound is a substrate of serum amine oxidase. Both oxa-Spm and oxa-Spd caused cell shrinkage, as determined by phase-contrast microscopy. After incubation with 10 microM of either compound for 8 h, the cells underwent chromatin condensation and nuclear fragmentation. However, no clear DNA ladder was obtained by electrophoresis. The sulphonamido oxa-polyamine derivatives and especially oxa-Spd enhanced the activity of polyamine oxidase (PAO), an enzyme capable of oxidising N1-acetylated spermine and spermidine to spermidine and **putrescine**, respectively, generating cytotoxic H2O2 and 3-acetamidopropanal as by-products. The intracellular polyamine content was only marginally reduced in response to drug treatment. In conclusion, our data show that these novel sulphonamido oxa-polyamine derivatives possess high cytotoxic activity against MCF-7 cells and indicate that induction of PAO may mediate their cytotoxicity via **apoptosis**.

21/3,AB/7 (Item 7 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

13215800 21974859 PMID: 11978014

Polyamine depletion induces **apoptosis** through mitochondria-mediated pathway.

Nitta Takeshi; Igarashi Kazuei; Yamamoto Naoki

Department of Molecular Virology, Tokyo Medical and Dental University, Tokyo 113-8519, Japan.

Experimental cell research (United States) May 15 2002, 276 (1)

p120-8, ISSN 0014-4827 Journal Code: 0373226

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Polyamines, namely **putrescine**, spermidine, and spermine, are essential for cell survival and proliferation. A decrease in intracellular polyamine levels is associated with **apoptosis**. In this study, we used inhibitors of polyamine biosynthesis to examine the effect of polyamine depletion. A combination of inhibitors of ornithine decarboxylase, S-adenosylmethionine decarboxylase, or spermidine synthase decreased intracellular polyamine levels and induced cell death in a WEHI231 murine B cell line. These cells exhibited apoptotic features including chromatin condensation and oligonucleosomal DNA fragmentation. Addition of exogenous polyamines reversed the observed features of apoptotic cell death. Similar effects were also observed in other cell lines: a human B cell line Ramos and a human T cell line Jurkat. Depletion of polyamines induced activation of caspase-3 and disruption of the mitochondrial membrane potential ($\Delta\psi$ m). Inhibition of caspase activities by an inhibitor prevented the apoptotic nuclear changes but not $\Delta\psi$ m disruption induced by polyamine depletion. Overexpression of Bcl-xL, an anti-apoptotic Bcl-2 family protein, completely inhibited $\Delta\psi$ m disruption, caspase

activation, and cell death. These results indicate that the depletion of intracellular polyamines triggers the mitochondria-mediated pathway for **apoptosis**, resulting in caspase activation and apoptotic cell death.

21/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12709975 21588253 PMID: 11590175

Polyamine depletion induces rapid NF-kappa B activation in IEC-6 cells.

Pfeffer L M; Yang C H; Murti A; McCormack S A; Viar M J; Ray R M; Johnson L R

Department of Pathology, University of Tennessee Health Science Center, Memphis, Tennessee 38163, USA. lpfeffer@utmem.edu

Journal of biological chemistry (United States) Dec 7 2001, 276 (49)

p45909-13, ISSN 0021-9258 Journal Code: 2985121R

Contract/Grant No.: CA73753; CA; NCI; DK-16505; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The proliferation of the rat intestinal mucosal IEC-6 cell line requires polyamines, whose synthesis is catalyzed by the enzyme ornithine decarboxylase (ODC). ODC inhibition leads to polyamine depletion, as well as inhibition of both cell proliferation and **apoptosis** by regulating gene expression. The NF-kappa B transcription factor regulates genes involved in apoptotic, immune, and inflammatory responses. In the present study we tested the hypothesis that NF-kappa B is activated following ODC inhibition. We found that the inhibition of ODC by alpha-difluoromethylornithine (DFMO) resulted in a approximately 50% decrease in intracellular **putrescine** levels within 1 h. NF-kappa B is activated by DFMO through the degradation of the inhibitory protein I kappa B alpha that sequesters NF-kappa B in the cytoplasm. The DFMO-induced NF-kappa B complexes contain the p65 and p50 members of the Rel protein family. DFMO-induced NF-kappa B activation was accompanied by the translocation of p65 from the cytoplasm into the nucleus. DFMO selectively inhibited a gene reporter construct dependent on the kappa B site present in the HLA-B7 gene. In contrast, DFMO had no effect on a gene reporter construct dependent on the kappa B site present in the interleukin-8 gene. Thus, we report that ODC inhibition activates the NF-kappa B transcription factor, which may mediate the altered physiological state of intestinal cells that occurs following polyamine depletion.

21/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12609999 21554983 PMID: 11697888

Transglutaminase activity is involved in polyamine-induced programmed cell death.

Facchiano F; D'Arcangelo D; Ricconi A; Lentini A; Beninati S; Capogrossi M C

Laboratorio di Patologia Vascolare, Istituto Dermatologico dell'Immacolata, Rome, Italy. f.facchiano@idi.it

Experimental cell research (United States) Nov 15 2001, 271 (1)

p118-29, ISSN 0014-4827 Journal Code: 0373226

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Natural polyamines, i.e., **putrescine**, spermidine, and spermine, are ubiquitous molecules essential for cell proliferation and differentiation. In the present study, the effect of polyamines on primary cultures of bovine aortic endothelial cells (BAECs), rat aortic smooth muscle cells

(RASMCs), and a human melanoma cell line was examined. While in the absence of fetal calf serum (FCS) polyamines had no effect on viability, in the presence of FCS spermidine and spermine, at concentrations close to physiologic levels, induced a dose-dependent cell death, whereas **putrescine** was ineffective. RASMCs were significantly more sensitive than other cells. FACS analysis, oligo-nucleosome ELISA, Hoechst nuclear staining, and Annexin V-FITC quantification showed that cell death was likely due to **apoptosis**. Cells exposed to spermidine showed a marked increase of intracellular transglutaminase (TGase) activity (approximately 30-fold over control). Inhibitors of polyamine oxidation or inhibitors of TGase activity prevented polyamine-induced **apoptosis**. Moreover, tissue TGase overexpression significantly increased cell sensitivity to polyamine, suggesting that this effect is likely related to enhanced intracellular TGase activity. These data indicate that polyamines may modulate cell viability through a novel TGase-dependent process. Copyright 2001 Academic Press.

21/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12597576 21538629 PMID: 11682054

Oxidation products of polyamines induce mitochondrial uncoupling and cytochrome c release.

Maccarrone M; Bari M; Battista N; Di Rienzo M; Falciglia K; Finazzi Agro A

Department of Experimental Medicine and Biochemical Sciences, University of Rome 'Tor Vergata', Via di Tor Vergata 135, I-00133, Rome, Italy.

FEBS letters (Netherlands) Oct 19 2001, 507 (1) p30-4, ISSN 0014-5793 Journal Code: 0155157

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Spermine is shown to uncouple isolated mitochondria and to trigger the selective release of cytochrome c. Pargyline, an inhibitor of amine oxidase (AO), fully prevented these effects of spermine, which instead were potentiated by exogenous AO. Hydrogen peroxide, an oxidation product of spermine, mimicked the effects of spermine on mitochondria, while the addition of catalase prevented them. Spermidine and **putrescine** also caused mitochondrial uncoupling and triggered cytochrome c release, with a potency which correlated with the substrate preference of mitochondrial AO. Pargyline protected human lymphoma U937 cells against UVB-induced **apoptosis**, by reducing AO activity, mitochondrial uncoupling and cytochrome c release.

21/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11353273 21424638 PMID: 11533243

The ornithine decarboxylase gene is essential for cell survival during early murine development.

Pendeville H; Carpino N; Marine J C; Takahashi Y; Muller M; Martial J A; Cleveland J L

Department of Biochemistry, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.

Molecular and cellular biology (United States) Oct 2001, 21 (19) p6549-58, ISSN 0270-7306 Journal Code: 8109087

Contract/Grant No.: CA-21765; CA; NCI; CA76379; CA; NCI; DK44158; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Overexpression and inhibitor studies have suggested that the c-Myc target gene for ornithine decarboxylase (ODC), the enzyme which converts ornithine to **putrescine**, plays an important role in diverse biological processes, including cell growth, differentiation, transformation, and **apoptosis**. To explore the physiological function of ODC in mammalian development, we generated mice harboring a disrupted ODC gene. ODC-heterozygous mice were viable, normal, and fertile. Although zygotic ODC is expressed throughout the embryo prior to implantation, loss of ODC did not block normal development to the blastocyst stage. Embryonic day E3.5 ODC-deficient embryos were capable of uterine implantation and induced maternal decidualization yet failed to develop substantially thereafter. Surprisingly, analysis of ODC-deficient blastocysts suggests that loss of ODC does not affect cell growth per se but rather is required for survival of the pluripotent cells of the inner cell mass. Therefore, ODC plays an essential role in murine development, and proper homeostasis of polyamine pools appears to be required for cell survival prior to gastrulation.

21/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11335118 21393593 PMID: 11502571

Polyamine depletion stabilizes p53 resulting in inhibition of normal intestinal epithelial cell proliferation.

Li L; Rao J N; Guo X; Liu L; Santora R; Bass B L; Wang J Y

Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.

American journal of physiology. Cell physiology (United States) Sep 2001, 281 (3) pC941-53, ISSN 0363-6143 Journal Code: 100901225

Contract/Grant No.: DK57819; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The p53 nuclear phosphoprotein plays a critical role in transcriptional regulation of target genes involved in growth arrest and **apoptosis**. The natural polyamines, including spermidine, spermine, and their precursor **putrescine**, are required for cell proliferation, and decreasing cellular polyamines inhibits growth of the small intestinal mucosa. In the current study, we investigated the mechanisms of regulation of p53 gene expression by cellular polyamines and further determined the role of the gene product in the process of growth inhibition after polyamine depletion. Studies were conducted both in vivo and in vitro using rats and the IEC-6 cell line, derived from rat small intestinal crypt cells. Levels for p53 mRNA and protein, transcription and posttranscription of the p53 gene, and cell growth were examined. Depletion of cellular polyamines by treatment with alpha-difluoromethylornithine (DFMO) increased p53 gene expression and caused growth inhibition in the intact small intestinal mucosa and the cultured cells. Polyamine depletion dramatically increased the stability of p53 mRNA as measured by the mRNA half-life but had no effect on p53 gene transcription in IEC-6 cells. Induction of p53 mRNA levels in DFMO-treated cells was paralleled by an increase in the rate of newly synthesized p53 protein. The stability of p53 protein was also increased after polyamine depletion, which was associated with a decrease in Mdm2 expression. When polyamine-deficient cells were exposed to exogenous spermidine, a decrease in p53 gene expression preceded an increase in cellular DNA synthesis. Inhibition of the p53 gene expression by using p53 antisense oligodeoxynucleotides significantly promoted cell growth in the presence of DFMO. These findings indicate that polyamines downregulate p53 gene expression posttranscriptionally and that growth inhibition of small intestinal mucosa after polyamine depletion is mediated, at least partially, through the activation of p53 gene.

21/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11274773 21309940 PMID: 11404465

L-arginine-dependent suppression of **apoptosis** in *Trypanosoma cruzi*: contribution of the nitric oxide and polyamine pathways.

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Proceedings of the National Academy of Sciences of the United States of America (United States) Jun 19 2001, 98 (13) p7301-6, ISSN 0027-8424
Journal Code: 7505876

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Until recently, a capacity for **apoptosis** and synthesis of nitric oxide (*NO) were viewed as exclusive to multicellular organisms. The existence of these processes in unicellular parasites was recently described, with their biological significance remaining to be elucidated. We have evaluated L-arginine metabolism in *Trypanosoma cruzi* in the context of human serum-induced apoptotic death. **Apoptosis** was evidenced by the induction of DNA fragmentation and the inhibition of [3H]thymidine incorporation, which were inhibited by the caspase inhibitor Ac-Asp-Glu-Val-aspartic acid aldehyde (DEVD-CHO). In *T. cruzi* exposed to death stimuli, supplementation with L-arginine inhibited DNA fragmentation, restored [3H]thymidine incorporation, and augmented parasite *NO production. These effects were inhibited by the *NO synthase inhibitor N(omega)-nitroarginine methyl ester (L-NAME). Exogenous *NO limited DNA fragmentation but did not restore proliferation rates. Because L-arginine is also a substrate for arginine decarboxylase (ADC), and its product agmatine is a precursor for polyamine synthesis, we evaluated the contribution of polyamines to limiting **apoptosis**. Addition of agmatine, **putrescine**, and the polyamines spermine and spermidine to *T. cruzi* sustained parasite proliferation and inhibited DNA fragmentation. Also, the ADC inhibitor difluoromethylarginine inhibited L-arginine-dependent restoration of parasite replication rates, while the protection from DNA fragmentation persisted. In aggregate, these results indicate that *T. cruzi* epimastigotes can undergo programmed cell death that can be inhibited by L-arginine by means of (i) a *NO synthase-dependent *NO production that suppresses **apoptosis** and (ii) an ADC-dependent production of polyamines that support parasite proliferation.

21/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11270378 21301750 PMID: 11408542

Geraniol, a component of plant essential oils, inhibits growth and polyamine biosynthesis in human colon cancer cells.

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Journal of pharmacology and experimental therapeutics (United States)
Jul 2001, 298 (1) p197-200, ISSN 0022-3565 Journal Code: 0376362

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Geraniol and other monoterpenes found in essential oils of fruits and herbs have been suggested to represent a new class of agents for cancer chemoprevention. As a first step in clarifying the mode of action of

geraniol on colon carcinogenesis, we studied its effects on the growth of a human colon cancer cell line (Caco-2). Geraniol (400 microM) caused a 70% inhibition of cell growth, with cells accumulating in the S transition phase of the cell cycle, and concomitant inhibition of DNA synthesis. No signs of cytotoxicity or **apoptosis** were detected. Geraniol caused a 50% decrease of ornithine decarboxylase activity, a key enzyme of polyamine biosynthesis, which is enhanced in cancer growth. This led to a 40% reduction of the intracellular pool of **putrescine**. Geraniol also activated the intracellular catabolism of polyamines, indicated by enhanced polyamine acetylation. These observations indicate that polyamine metabolism is presumably a target in the antiproliferative properties of geraniol.

21/3,AB/15 (Item 15 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11177024 21198522 PMID: 11303587

Alpha-difluoromethylornithine induction of **apoptosis**: a mechanism which reverses pre-established cell proliferation and cancer initiation in esophageal carcinogenesis in zinc-deficient rats.

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Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology (United States) Mar 2001, 10 (3) p191-9, ISSN 1055-9965 Journal Code: 9200608

Contract/Grant No.: GM-26290; GM; NIGMS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Alpha-difluoromethylornithine (DFMO) is an irreversible inhibitor of ornithine decarboxylase, the first enzyme in polyamine synthesis. Previous work showed simultaneous administration of DFMO and a zinc-deficient (ZD) diet to weanling rats from the beginning inhibited the onset of zinc-deficiency-induced esophageal cell proliferation by activating **apoptosis** and reduced the incidence of N-nitrosomethylbenzylamine (NMBA)-induced esophageal cancer. Because esophageal cancer initiation by NMBA is very rapid in ZD rats, this study determined whether DFMO is effective in preventing esophageal carcinogenesis when administered after the establishment of a carcinogenic environment. Weanling rats were given a ZD diet for 5 weeks to establish sustained increased esophageal cell proliferation and then an intragastric dose of NMBA. Thereafter, 20 rats were switched to DFMO-containing water while nine control ZD animals remained on deionized water; all of the animals continued on the ZD diet. Esophagi were collected 15 weeks later. The upper portion was processed for immunohistochemical analysis of cell proliferation, **apoptosis**, and expression of related genes, and the lower was processed for polyamine content. DFMO substantially reduces the levels of esophageal **putrescine** and spermidine and esophageal tumor incidence from 89 to 10% in ZD rats. Importantly, DFMO-treated ZD esophagi display increased rate of **apoptosis** accompanied by intense bax expression and greatly reduced cell proliferation by proliferating cell nuclear antigen expression. In addition, the p16(ink4a)/retinoblastoma control at G1 to S, deregulated in ZD esophagi, is restored after DFMO treatment. These results demonstrate that DFMO, a highly effective chemopreventive agent in esophageal carcinogenesis, reverses and counteracts esophageal cell proliferation/cancer initiation in ZD animals by way of stimulating **apoptosis**.

21/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11176873 21189624 PMID: 11292609

NF-kappaB activation and susceptibility to **apoptosis** after polyamine depletion in intestinal epithelial cells.

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American journal of physiology. Gastrointestinal and liver physiology (United States) May 2001, 280 (5) pG992-G1004, ISSN 0193-1857

Journal Code: 100901227

Contract/Grant No.: DK-57819; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The maintenance of intestinal mucosal integrity depends on a balance between cell renewal and cell death, including **apoptosis**. The natural polyamines, **putrescine**, spermidine, and spermine, are essential for mucosal growth, and decreasing polyamine levels cause G(1) phase growth arrest in intestinal epithelial (IEC-6) cells. The present study was done to determine changes in susceptibility of IEC-6 cells to **apoptosis** after depletion of cellular polyamines and to further elucidate the role of nuclear factor-kappaB (NF-kappaB) in this process. Although depletion of polyamines by alpha-difluoromethylornithine (DFMO) did not directly induce **apoptosis**, the susceptibility of polyamine-deficient cells to staurosporine (STS)-induced **apoptosis** increased significantly as measured by changes in morphological features and internucleosomal DNA fragmentation. In contrast, polyamine depletion by DFMO promoted resistance to apoptotic cell death induced by the combination of tumor necrosis factor-alpha (TNF-alpha) and cycloheximide. Depletion of cellular polyamines also increased the basal level of NF-kappaB proteins, induced NF-kappaB nuclear translocation, and activated the sequence-specific DNA binding activity. Inhibition of NF-kappaB binding activity by sulfasalazine or MG-132 not only prevented the increased susceptibility to STS-induced **apoptosis** but also blocked the resistance to cell death induced by TNF-alpha in combination with cycloheximide in polyamine-deficient cells. These results indicate that 1) polyamine depletion sensitizes intestinal epithelial cells to STS-induced **apoptosis** but promotes the resistance to TNF-alpha-induced cell death, 2) polyamine depletion induces NF-kappaB activation, and 3) disruption of NF-kappaB function is associated with altered susceptibility to **apoptosis** induced by STS or TNF-alpha. These findings suggest that increased NF-kappaB activity after polyamine depletion has a proapoptotic or antiapoptotic effect on intestinal epithelial cells determined by the nature of the death stimulus.

21/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11168091 21214575 PMID: 11313919

Regulation of estrogenic and nuclear factor kappa B functions by polyamines and their role in polyamine analog-induced **apoptosis** of breast cancer cells.

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Oncogene (England) Mar 29 2001, 20 (14) p1715-29, ISSN 0950-9232

Journal Code: 8711562

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Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The natural polyamines **putrescine**, spermidine, and spermine- are essential for cell growth and differentiation. Polyamines are involved in several gene regulatory functions, although their mechanism(s) of action has not been elucidated. We investigated the role of polyamines in the function of NF-kappa B and estrogen receptor-alpha (ER alpha), two transcription factors implicated in breast cancer cell proliferation and cell survival, using MCF-7 breast cancer cells. We found that spermine facilitated the binding of ER alpha and NF-kappa B to estrogen response element (ERE)- and NF-kappa B response element (NRE), respectively, and enhanced ER alpha-mediated transcriptional activation in transient transfection experiments. We also found that the association of the co-regulatory protein CBP/p300 with ER alpha and NF-kappa B was increased by spermine treatment of MCF-7 cells. Spermine also increased the nuclear translocation of NF-kappa B compared to the control. In contrast, treatment of MCF-7 cells with polyamine analogs, BE-3-4-3 and BE-3-3-3, resulted in transcriptional inhibition of both ERE- and NRE-driven reporter plasmids. In addition, polyamine analogs inhibited the association of ER alpha and NF-kappa B with CBP/p300 and were unable to facilitate nuclear translocation of NF-kappa B. APO-BRDU assay demonstrated that polyamine analogs induced **apoptosis**, with a loss of the anti-apoptotic protein Bcl-2. These data show a gene regulatory function of polyamines involving transcriptional activation of ER alpha and NF-kappa B, potentially leading to the up-regulation of genes involved in breast cancer cell proliferation. Our results with BE-3-4-3 and BE-3-3-3 suggest that down-regulation of ER alpha- and NF-kappa B-regulated genes is a possible mechanism for the action of polyamine analogs in inducing **apoptosis** of breast cancer cells.

21/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11158866 21179016 PMID: 11281655

Involvement of polyamines in B cell receptor-mediated **apoptosis**: spermine functions as a negative modulator.

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Department of Microbiology and Molecular Virology, Tokyo Medical and Dental University, Tokyo, Japan.

Experimental cell research (United States) Apr 15 2001, 265 (1)
p174-83, ISSN 0014-4827 Journal Code: 0373226

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The B cell lymphoma WEHI231 has been used as a model for studying clonal deletion of B cells on the basis of its ability to undergo growth arrest and **apoptosis** by B cell antigen receptor (BCR) cross-linking. To comprehensively analyze the genes involved in BCR-mediated **apoptosis**, we applied the technique of serial analysis of gene expression (SAGE) to WEHI231. Comparison of expression patterns revealed that BCR cross-linking caused coordinate changes in the expression of genes involved in polyamine metabolism. Polyamines are ubiquitous compounds required for cell proliferation and homeostasis. The coordinate expression of the polyamine-related genes was confirmed by semiquantitative reverse transcriptase-polymerase chain reaction analysis. During **apoptosis**, the genes involved in polyamine biosynthesis were downregulated, whereas those involved in polyamine catabolism were upregulated, suggesting that intracellular polyamines play a role in BCR-mediated **apoptosis**. Levels of intracellular **putrescine**, spermidine, and spermine were reduced after BCR cross-linking. These effects were prevented by concurrent

CD40 stimulation, which blocked BCR-mediated **apoptosis**. Furthermore, addition of spermine could repress the BCR-mediated **apoptosis** by attenuating the mitochondrial membrane potential (Deltapsim) loss and activation of caspase-7 induced by BCR signaling. These findings strongly suggest that polyamine regulation is involved in **apoptosis** during B cell clonal deletion. Copyright 2001 Academic Press.

21/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11147891 21157044 PMID: 11256964

Effect of polyamine depletion on caspase activation: a study with spermine synthase-deficient cells.

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Biochemical journal (England) Apr 1 2001, 355 (Pt 1) p199-206, ISSN 0264-6021 Journal Code: 2984726R

Contract/Grant No.: CA-18138; CA; NCI; GM-26290; GM; NIGMS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Activation of the caspase proteases represents a central point in **apoptosis**. The requirement for spermine for the processes leading to caspase activation has been studied in transformed embryonic fibroblasts obtained from gyro (Gy) mutant male mice. These cells lack spermine synthase activity and thus provide a valuable model to study the role of spermine in cell processes. Gy fibroblasts do not contain spermine and have a higher spermidine content. However, when compared with fibroblasts obtained from normal male littermates (N cells), Gy fibroblasts were observed to grow normally. The lack of spermine did not affect the expression of Bcl-2, and caspases 3 and 9 were activated by etoposide in both N and Gy cells, indicating that spermine is dispensable for caspase activation. Spermine deficiency did not significantly influence caspase activity in cells treated with etoposide, cycloheximide or staurosporine, but sensitized the cells to UV irradiation, which triggered significantly higher caspase activity in Gy cells compared with N cells. alpha-Difluoromethylornithine (DFMO), an inhibitor of polyamine synthesis that is able to deplete cells of **putrescine** and spermidine, but usually does not influence spermine content, was able to produce a more complete polyamine depletion in Gy cells. This depletion, which included spermine deficiency, dramatically increased caspase activation and cell death in Gy fibroblasts exposed to UV irradiation. On the other hand, in either N or Gy cells, DFMO treatment did not influence caspase activity triggered by staurosporine, but inhibited it when the inducers were cycloheximide or etoposide. In Gy cells depleted of polyamines by DFMO, polyamine replenishment with either spermidine or spermine was sufficient to restore caspase activity induced by etoposide, indicating that, in this model, polyamines have an interchangeable role in supporting caspase activation. Therefore, spermine is not required for such activation, and the effect and specificity of polyamine depletion on caspase activity may be very different, depending on the role of polyamines in the specific death pathways engaged by different stimuli. Some inducers of **apoptosis**, for example etoposide, absolutely require polyamines for caspase activation, yet the lack of polyamines, particularly spermine, strongly increases caspase activation when induced by UV irradiation.

21/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11118639 21126367 PMID: 11223914

Role of spermine in amyloid beta-peptide-associated free radical-induced neurotoxicity.

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Journal of neuroscience research (United States) Mar 1 2001, 63 (5)
p395-401, ISSN 0360-4012 Journal Code: 7600111

Contract/Grant No.: AG-05119; AG; NIA; AG-10836; AG; NIA; CA58935; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The polyamines, relatively low-molecular-weight aliphatic compounds, are the main inducers of eukaryotic cell growth and proliferation. Although polyamine requirements for cell growth are well defined, their role is still enigmatic. We have previously reported that amyloid beta-peptide (A beta), the main constituent of senile plaques in Alzheimer's disease (AD) brain, is toxic to neurons through a free radical-dependent oxidative stress mechanism and that A beta(1-42), the principal form of A beta in AD brain, causes an increase in polyamine metabolism manifested by up-regulated polyamine uptake and increased ornithine decarboxylase (ODC) activity. Both effects were prevented by the free radical scavenger vitamin E. Spermine has been reported to function directly as a free radical scavenger. In the current study, we aimed to address whether up-regulation of polyamine metabolism is a defense against, or a result of, A beta-induced oxidative stress by investigating the capability of spermine to quench A beta-associated free radicals in solution and to assert a protective function of spermine in neuronal culture against A beta. Pretreatment of cultured neurons with spermine prior to A beta exposure failed to prevent A beta-induced cell death. Indeed, A beta plus spermine added to cultured neurons was even more neurotoxic than either agent alone. Additionally, inhibition of the polyamine synthesis by difluoromethylornithine (DFMO) did not protect cells from A beta-induced free radical toxicity, and stimulation of the synthesis of putrescine and spermine by the aminopropyltransferase inhibitor S-adenosyl-1,8-diamino-thiooctane (AdoDATO), rather, further enhanced A beta-induced toxicity. Although spermine is capable of scavenging free radicals generated by A beta in solution as measured by electron paramagnetic resonance (EPR) spectroscopy, the up-regulated transport of exogenously added spermine together with A beta may lead to overaccumulation of a cellular spermine pool, with resulting enhanced neurotoxicity. Copyright 2001 Wiley-Liss, Inc.

21/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10908228 20464675 PMID: 11012080

Molecular correlates of the action of bis(ethyl)polyamines in breast cancer cell growth inhibition and apoptosis.

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Biochemistry and cell biology = Biochimie et biologie cellulaire (CANADA)

2000, 78 (4) p415-26, ISSN 0829-8211 Journal Code: 8606068

Contract/Grant No.: ES05022; ES; NIEHS; RO1 CA42439; CA; NCI; RO1 CA73058; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Polyamines are known to be involved in cell growth regulation in breast cancer. To evaluate the efficacy of bis(ethyl)polyamine analogs for breast cancer therapy and to understand their mechanism of action we measured the effects of a series of polyamine analogs on cell growth, activities of enzymes involved in polyamine metabolism, intracellular polyamine levels, and the uptake of putrescine and spermidine using MCF-7 breast cancer cells. The IC50 values for cell growth inhibition of three of the compounds, N1,N12-bis(ethyl)spermine, N1,N11-bis(ethyl)norspermine, and N1,N14-bis(ethyl)homospermine, were in the range of 1-2 microM. Another group of three compounds showed antiproliferative activity at about 5 microM level. These compounds are also capable of suppressing colony formation in soft agar assay and inducing apoptosis of MCF-7 cells. The highly effective growth inhibitory agents altered the activity of polyamine biosynthetic and catabolic enzymes and down-regulated the transport of natural polyamines, although each compound produced a unique pattern of alterations in these parameters. HPLC analysis showed that cellular uptake of bis(ethyl)polyamines was highest for bis(ethyl)spermine. We also analyzed polyamine analog conformations and their binding to DNA minor or major grooves by molecular modelling and molecular dynamics simulations. Results of these analyses indicate that tetramine analogs fit well in the minor groove of DNA whereas, larger compounds extend out of the minor groove. Although major groove binding was also possible for the short tetramine analogs, this interaction led to a predominantly bent conformation. Our studies show growth inhibitory activities of several potentially important analogs on breast cancer cells and indicate that multiple sites are involved in the mechanism of action of these analogs. While the activity of an analog may depend on the sum of these different effects, molecular modelling studies indicate a correlation between antiproliferative activity and stable interactions of the analogs with major or minor grooves of DNA.

21/3,AB/22 (Item 22 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

10825404 20372235 PMID: 10917567

Spermine cytotoxicity to human colon carcinoma-derived cells (CaCo-2).

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Cell biology and toxicology (NETHERLANDS) 2000, 16 (2) p117-30,

ISSN 0742-2091 Journal Code: 8506639

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Spermine is a constituent of all vertebrate cells. Nevertheless, it exerts toxic effects if it accumulates in cells. Spermine is a natural substrate of the FAD-dependent polyamine oxidase, a constitutive enzyme of many cell types. It has been reported that the toxicity of spermine was enhanced if polyamine oxidase was inhibited. We were interested to examine spermine toxicity to human colon carcinoma-derived CaCo-2 cells because, in contrast to most tumor cell lines, CaCo-2 cells undergo differentiation, which is paralleled by changes in polyamine metabolism. CaCo-2 cells were remarkably resistant to spermine accumulation, presumably because spermine is degraded by polyamine oxidase at a rate sufficient to provide spermidine for the maintenance of growth. Inactivation of polyamine oxidase increased the sensitivity to spermine. A major reason for the enhanced spermine cytotoxicity at low polyamine oxidase activity is presumably the profound depletion of spermidine, and the consequent occupation of spermidine binding sites by spermine. Hydrogen peroxide and the aldehydes 3-aminopropanal and 3-acetamidopropanal, the products of polyamine

oxidase-catalyzed splitting of spermine and N1-acetylspermine, contribute little to spermine cytotoxicity. Activation of caspase by spermine was insignificant, and the formation of DNA ladders, another indicator of apoptotic cell death, could not be observed. Thus it appears that cell death due to excessive accumulation of spermine in CaCo-2 cells was mainly nonapoptotic. The content of brush border membranes did not change between days 6 and 8 after seeding, and it was not affected by exposure of the cells to spermine. However, the activities of alkaline phosphatase, sucrase, and aminopeptidase in nontreated cells were considerably enhanced during this period, but remained low if cells were exposed to spermine. These changes appear to indicate that differentiation is prevented by intoxication with spermine, although other explanations cannot be excluded.

21/3,AB/23 (Item 23 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10805470 20362171 PMID: 10904546

Apoptosis is regulated by polyamines in the cell cycle of Chinese hamster ovary cells.

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Biocell : official journal of the Sociedades Latinoamericanas de Microscopia Electronica ... et. al (ARGENTINA) Dec 1999, 23 (3) p223-8
ISSN 0327-9545 Journal Code: 9438655

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

This paper deals with the relationship between the polyamine metabolism and **apoptosis** in the different phases of the cell cycle in a Chinese hamster ovary (CHO) cell line. Synchronously growing cells were obtained by the addition of 1.2 mM hydroxyurea and the progression through the cell cycle was monitored by determining the incorporation of 3H-thymidine in the DNA. Ornithine decarboxylase (ODC) activity showed a peak in S phase, while intracellular **putrescine** and spermine contents increased constantly, reaching to a maximum level at G2 phase; spermidine content doubled during G2 and increased four times during M, compared to G1. The increment in the endogenous polyamine content was associated to a diminished uptake from the medium. The apoptotic index was higher in G2 phase, coinciding with the maximum level observed in **putrescine** content. The results support the idea that intracellular **putrescine** level is closely related to **apoptosis**.

21/3,AB/24 (Item 24 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10795176 20344185 PMID: 10888272

Involvement of polyamines in **apoptosis**. Facts and controversies: effectors or protectors?

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Seminars in cancer biology (UNITED STATES) Feb 2000, 10 (1) p55-68,
ISSN 1044-579X Journal Code: 9010218

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The natural polyamines (**putrescine**, spermidine and spermine) are ubiquitous low-molecular aliphatic amines that play multifunctional roles in cell growth and differentiation. Recently, evidence has merging that

polyamines are actively involved in cell death. Changes in polyamine homeostasis have been reported during cell death of nerve cells, in programmed cell death of embryonic cells and in various in vitro models of **apoptosis**. Polyamines and many of their structural analogs exert cytotoxic effects in vitro as well in vivo. Furthermore, polyamine analogs and inhibitors of the polyamine anabolic/catabolic pathways modulate processes of cell death in a cell-type specific way. Much ambiguity exists in the working mechanisms by which polyamines mediate **apoptosis** since they have been shown to act as promoting, modulating or protective agents in **apoptosis**. Nevertheless, from the studies reviewed here it can be concluded that polyamines are critically involved in cellular survival which makes them suitable targets for therapeutic intervention that is specifically directed to cell death pathways.

21/3,AB/25 (Item 25 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10656514 20193301 PMID: 10731035

Long chain diamines inhibit growth of C6 glioma cells according to their hydrophobicity. An in vitro and molecular modeling study.

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Naunyn-Schmiedeberg's archives of pharmacology (GERMANY) Mar 2000, 361

(3) p235-46, ISSN 0028-1298 Journal Code: 0326264

Contract/Grant No.: CA73058; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

A series of diamines with the general structure $\text{NH}_2(\text{CH}_2)_x\text{NH}_2$, $x=2-12$, was tested for their potential effects on cell proliferation of cultured rat C6 glioma cells in comparison to natural polyamines. Long chain diamines reduced cell number after 48 h in culture with a sequence of 1,12-diaminododecane (1,12-DD) $>1,10$ -diaminodecane $>1,9$ -diaminononane. Polyamines (**putrescine**, spermidine and spermine) as well as diamines up to a CH_2 -chain length of $x=8$ were found to be ineffective. The spermine analogue 1,12-DD was the most effective molecule in reducing cell number in an irreversible, dose-dependent manner ($\text{EC}_{50}=3$ μM under serum-free conditions). In further experiments we investigated the mechanisms of action of 1,12-DD. The compound had only a minor effect on cell cycle and did not affect free internal calcium concentration. Under physiological conditions 1,12-DD interacts with triplex DNA but not with duplex DNA. Ornithine decarboxylase activity as well as the concentration of internal polyamines were found to be reduced by 1,12-DD. Polyamine application, however, was not able to reverse the effect of 1,12-DD, indicating a polyamine-independent or non-competitive mechanism of action. 1,12-DD reduced cell number by induction of **apoptosis** as well as necrosis. In molecular modeling studies it was found that a minimal hydrophobic intersegment of at least 4 A was required to make a diamine an effective drug in respect to cellular growth. A hydrophobic gap of this size fits the minimum requirement expected from molecular modeling to provide space for hydrophobic interactions with parts of proteins like a CH_3 -group. Our results show that 1,12-DD acts as a potent drug, reducing the number of C6 glioma cells, and suggest that its spatial and hydrophobic properties are responsible for its mechanism of action.

21/3,AB/26 (Item 26 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10645608 20164053 PMID: 10698696

Antizyme inhibitor is rapidly induced in growth-stimulated mouse fibroblasts and releases ornithine decarboxylase from antizyme suppression.

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Biochemical journal (ENGLAND) Mar 15 2000, 346 Pt 3 p699-704, ISSN 0264-6021 Journal Code: 2984726R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Ornithine decarboxylase (ODC) catalyses the first step in the synthesis of the polyamines **putrescine**, spermidine and spermine. The polyamines are essential for cell growth, but at elevated levels they may be tumorigenic, toxic, or may induce **apoptosis**. Therefore, ODC activity is highly regulated. It is induced when cells are stimulated to grow, and it is subjected to feedback inhibition by the polyamines. By causing ribosomal frameshifting, polyamines induce the synthesis of antizyme, a 23-kDa protein, which binds to ODC, inhibits its activity and promotes its degradation by the 26 S proteasome. Antizyme, in turn, is inhibited by antizyme inhibitor (AZI). We describe the cloning of a mouse AZI cDNA, encoding a protein with high homology to mouse ODC. Using purified recombinant proteins, we show that AZI (which has no ODC activity) can release enzymically active ODC from antizyme suppression *in vitro*. We also show that ODC reactivation takes place in mouse fibroblasts upon transient transfection with an AZI-expressing plasmid construct. Finally we demonstrate that the AZI mRNA content of mouse fibroblasts increases significantly within an hour of growth stimulation, i.e. much earlier than ODC transcripts. Our results indicate that induction of AZI synthesis may represent a means of rescuing ODC molecules that have been inactivated and tagged for degradation by antizyme, when culture conditions improve and polyamine production is needed for cell growth and proliferation.

21/3,AB/27 (Item 27 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10592433 20133683 PMID: 10668504

Mammalian Cu-containing amine oxidases (CAOs): new methods of analysis, structural relationships, and possible functions.

Houen G

Statens Serum Institut.

APMIS. Supplementum (DENMARK) 1999, 96 p1-46, ISSN 0903-465X
Journal Code: 8812090

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

This thesis describes new and original experimental results on Cu-dependent amine oxidases (CAOs), which show that these enzymes can be conveniently and specifically detected *in situ* using a peroxidase-coupled activity staining method with 4-Cl-1-naphtole as hydrogen donor substrate. Even more sensitive *in situ* detection can be achieved using a chemiluminescence-based coupled peroxidase assay which was applied to show that human placenta CAO activity is confined to maternal vessels. A general purification scheme for CAOs is described, and applied to purification of different CAOs. Peptide maps and immunological crossreactivity studies with monoclonal antibodies raised against the purified enzymes showed that they were closely related. Amino acid sequence data for the bovine serum CAO showed that they form a separate group (E.C. 1.4.3.6) with no homology to other enzymes. A cDNA sequence was obtained on the basis of the amino acid sequence data, and this was found to encode a bovine lung CAO, related to bovine serum CAO. The genes for bovine lung and bovine serum CAO are characterized, and Southern blotting analysis of bovine chromosomal DNA

shows the existence of a least one more bovine CAO. The purification of human neutrophil CAO is attempted, but it is described how lactoferrin, a protein with many properties in common with CAOs, and with a low degree of sequence identity can account for many observations on human neutrophil CAO. The products of bovine serum CAO oxidation of polyamines are characterised, and 3-aminopropanal is found to be the principal aminoaldehyde produced. Finally, a polyamine-stimulated binding of human placenta CAO to single-stranded DNA is described, and it is reported that the DNA-bound CAO is enzymically active and that the oxidation of DNA-bound polyamines leads to degradation of DNA. In addition to the experimental results, the properties of polyamines and Cu-dependent amine oxidases are reviewed. The polyamines spermidine and spermine interact specifically with nucleic acids and several other molecules. They are synthesised from **putrescine**, which is a key regulatory molecule formed from ornithine by ornithine decarboxylase, a highly inducible and regulated enzyme. The polyamines can be converted to **putrescine** by CAOs or spermidine/spermine acetyltransferase and polyamine oxidase. **Putrescine** is degraded by CAOs, which are also involved in degradation of histamine, a mediator of inflammatory processes. CAOs catalyse the general reaction: $R1CH2NHR2 + O2 + H2O \rightarrow R1CHO + R2NH2 + H2O2$ and in addition to the catabolism of **putrescine** and histamine CAOs are involved in regulation of growth and **apoptosis** by to the generation of aminoaldehydes and hydrogen peroxide which have growth inhibitory properties. Several homologous CAOs have been purified and characterized and they form a family with two subgroups. They are homodimers with a relative molecular weight of 180,000 and contain Cu^{2+} and a modified tyrosine, topaquinone, in the active site. CAOs are present in most tissues with highest amounts in intestine, kidneys, liver and placenta, but the cellular distributions and functions of CAOs are still poorly described, partly due to the use of many different assays and partly due to a broad substrate specificity of the enzymes. However, polyamines and CAOs seem to form a universal system contributing to regulation of growth, differentiation, and **apoptosis**.

21/3,AB/28 (Item 28 from file: 155)
 DIALOG(R) File 155:MEDLINE(R)

10581533 20120220 PMID: 10656427

Effects of the polyamine analogues N1-ethyl-N11-((cyclopropyl)methyl)-4,8-diazaundecane and N1-ethyl-N11-((cycloheptyl)methyl)-4,8-diazaundecane in human prostate cancer cells.

McCloskey D E; Woster P M; Casero R A; Davidson N E

Pennsylvania State University College of Medicine, Hershey, USA.

Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Jan 2000, 6 (1) p17-23, ISSN 1078-0432 Journal Code: 9502500

Contract/Grant No.: CA 51085; CA; NCI; CA 58236; CA; NCI; CA 63552; CA; NCI; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The high levels of polyamines maintained in the prostate suggest that these compounds are important to prostate cell function and that disruption of polyamine metabolism may be an effective way to stop the growth of prostate cancer cells. The unsymmetrically alkylated polyamine analogues N1-ethyl-N11-((cyclopropyl)methyl)-4,8-diazaundecane (CPENSpm) and N1-ethyl-N11-((cycloheptyl)methyl)-4,8-diazaundecane (CHENSpm) have been shown previously to have cytotoxic effects in breast and non-small cell lung cancer cells. We have now investigated the responses of three human prostate cancer cell lines, LNCaP, PC3, and Du145, to these polyamine analogues and to the symmetrically alkylated analogue N1,N11-bis(ethyl)norspermine (BE 3-3-3). The Du145 cell line, in which IC50

values ranged from 0.65 to 0.8 microM, was the most sensitive to each of the polyamine analogues, although significant growth inhibition resulted in the other cell lines as well. CPENSp and BE 3-3-3 but not CHENSp caused significant decreases in the intracellular spermine and spermidine pools, although all three analogues accumulated to high levels in each of the cell lines. Spermidine/spermine N1-acetyltransferase activity was induced 23-250-fold in response to CPENSp and BE 3-3-3, but it was not affected by CHENSp. None of the analogues had significant effects on the activities of ornithine decarboxylase or S-adenosylmethionine decarboxylase. Quantitation of DNA fragmentation indicative of programmed cell death (PCD) showed that both CPENSp and CHENSp were effective inducers of PCD in all three prostate cell lines. In contrast, BE 3-3-3 led to PCD only in LNCaP cells. The ability to induce PCD was the only parameter measured that correlated with cell line sensitivity to these polyamine analogues.

21/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10306940 99297555 PMID: 10371145

Spermine triggers the activation of caspase-3 in a cell-free model of **apoptosis**.

Stefanelli C; Bonavita F; Stanic' I; Pignatti C; Flamigni F; Guarnieri C; Caldarera C M

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FEBS letters (NETHERLANDS) May 21 1999, 451 (2) p95-8, ISSN 0014-5793 Journal Code: 0155157

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Polyamines are ubiquitous organic cations required for cell proliferation. However, some evidence suggested that their excessive accumulation can induce **apoptosis**. We show here that, in a post-nuclear extract from U937 cells, the addition of spermine triggers the death program, represented by cytochrome c exit from mitochondria, the dATP-dependent processing of pro-caspase-3 and the onset of caspase activity. Spermine is more effective than spermidine, whereas **putrescine** has no effect. Polyamine acetylation abolishes their pro-apoptotic power. These data demonstrate a direct mechanism responsible for polyamine toxicity and also suggest that an excessive elevation of free polyamines could be involved in the transduction of a death signal.

21/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10230285 99216302 PMID: 10198235

2-deoxy-d-ribose-induced **apoptosis** in HL-60 cells is associated with the cell cycle progression by spermidine.

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Biochemical and biophysical research communications (UNITED STATES) Apr 13 1999, 257 (2) p460-5, ISSN 0006-291X Journal Code: 0372516

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The presence of polyamines is required for the apoptotic program triggered by 2-deoxy-D-ribose (dRib) in HL-60 cells, but their oxidative metabolites does not appear to be involved in the oxidative stress caused

by the sugar. The present study points to a relationship between spermidine-induced G1 to S phase transition and the onset of dRib-induced **apoptosis**. Conversely, the G1 block induced by alpha-difluoromethylornithine (DFMO) is associated with a protective effect against dRib-induced cell suicide. Replenishment of the intracellular spermidine pool by exogenous **putrescine** and spermidine induces cell cycle progression and restores apoptotic levels. The present data indicate that the induction of cell cycle progression by spermidine is a condition facilitating the activation of the apoptotic process by dRib. Copyright 1999 Academic Press.

21/3,AB/31 (Item 31 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10226588 99200678 PMID: 10102555

Polyamines found in the inflamed periodontium inhibit priming and **apoptosis** in human polymorphonuclear leukocytes.

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Journal of periodontology (UNITED STATES) Feb 1999, 70 (2) p179-84,
ISSN 0022-3492 Journal Code: 8000345

Contract/Grant No.: K04 DE00338; DE; NIDCR; RO1 DE09851; DE; NIDCR

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: Polymorphonuclear leukocytes (PMNs) are exposed to high concentrations of polyamines in the inflamed periodontium and possess a transport system for taking up these compounds. Previous studies suggest that polyamines are involved in priming of the PMN respiratory burst by tumor necrosis factor-alpha (TNF-alpha) and can stabilize DNA against degradation. The purpose of this study was to determine whether exogenous polyamines can modulate priming by TNF-alpha or delay nuclear changes associated with PMN **apoptosis** (programmed cell death). **METHODS:**

Isolated human PMNs were incubated with **putrescine** or spermidine in vitro. Superoxide generation was measured with a cytochrome C reduction assay, and apoptotic changes were assessed by fluorescence microscopy (after cell staining with acridine orange and ethidium bromide). **RESULTS:** Incubation with 1 mM **putrescine** for 1 hour inhibited superoxide production by TNF-primed PMNs by 20%, but enhanced the production of superoxide by unprimed cells by 38%. Both effects were dose dependent and statistically significant (P < 0.03, repeated measures ANOVA and Dunnett's test). Spermidine had no significant effects on PMN oxidative function.

With regard to **apoptosis**, 1 mM **putrescine** or spermidine produced a statistically significant reduction in the proportion of apoptotic PMNs within 6 to 9 hours (P < 0.05). In cells incubated for 7 hours with 300 microm **putrescine** or spermidine, the proportion of apoptotic cells was approximately 30% lower than in untreated controls (P < 0.05, Dunnett's test). The delay of **apoptosis** by spermidine was less profound than that produced by TNF-alpha and was not additive to the effects of this cytokine. **CONCLUSIONS:** Polyamines could potentially impair the priming of PMN oxidative function by TNF-alpha at sites where this cytokine is present. In the absence of TNF-alpha, polyamines could enhance PMN superoxide release and enhance the maintenance of PMN function in the periodontal pocket.

21/3,AB/32 (Item 32 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09915000 98345995 PMID: 9681017

Developmental expression and biochemical analysis of the Arabidopsis

atao1 gene encoding an H2O2-generating diamine oxidase.

Moller S G; McPherson M J

Centre for Plant Biochemistry and Biotechnology, University of Leeds, UK.

Plant journal : for cell and molecular biology (ENGLAND) Mar 1998, 13

(6) p781-91, ISSN 0960-7412 Journal Code: 9207397

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

A copper amine oxidase encoding gene, atao1, has been isolated and characterized from Arabidopsis thaliana. Sequence analysis reveals that atao1 encodes a 668 amino acid polypeptide (ATAO1) with 48% identity to copper amine oxidases from pea and lentil. The promoter region of atao1 was transcriptionally fused with the reporter genes encoding beta-glucuronidase and modified green fluorescent protein. Analysis of transgenic Arabidopsis together with in situ hybridization of wild-type plants reveals temporally and spatially discrete patterns of gene expression in lateral root cap cells, vascular tissue of roots, developing leaves, the hypocotyl, and in the style/stigmatal tissue. Enzyme activity assays show that ATA01 preferentially oxidizes the aliphatic diamine **putrescine** with production of the corresponding aldehyde, ammonia and hydrogen peroxide, a recognized plant signal molecule and substrate for peroxidases. Histochemical analysis reveals that atao1 expression in developing tracheary elements precedes and overlaps with lignification and therefore is a good marker for vascular development. In both vascular tissue and the root cap, atao1 expression occurs in cells destined to undergo programmed cell death.

21/3,AB/33 (Item 33 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

09697948 98124652 PMID: 9458319

The antiproliferative effect of HGF on hepatoma cells involves induction of **apoptosis** with increase in intracellular polyamine concentration levels.

Yanagawa K; Yamashita T; Yada K; Ohira M; Ishikawa T; Yano Y; Otani S; Sowa M

First Department of Surgery, Osaka City University, Medical School, 1-5-7 Asahimachi, Abenoku, Osaka 545, Japan.

Oncology reports (GREECE) Jan-Feb 1998, 5 (1) p185-90, ISSN 1021-335X Journal Code: 9422756

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Hepatocyte growth factor (HGF) induced **apoptosis** and decreased the DNA synthesis in Hep G2 cells. In the HGF group interleukin-1 converting enzyme, ornithine decarboxylase (ODC) activity and intracellular polyamine concentrations were increased compared to those of the control group. Administration of the ODC inhibitor decreased polyamine concentration, and inhibited apoptotic changes in the cells. These changes were reversed by exogenous addition of polyamine. These findings suggest that one of the mechanisms by which HGF exerts its antiproliferative effect is induction of **apoptosis** and that increase in intracellular polyamine concentration may be one of the triggers of cell death.

21/3,AB/34 (Item 34 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

09684193 98122570 PMID: 9462738

Suppression of aggregate formation and **apoptosis** by transglutaminase inhibitors in cells expressing truncated DRPLA protein

with an expanded polyglutamine stretch.

Igarashi S; Koide R; Shimohata T; Yamada M; Hayashi Y; Takano H; Date H; Oyake M; Sato T; Sato A; Egawa S; Ikeuchi T; Tanaka H; Nakano R; Tanaka K; Hozumi I; Inuzuka T; Takahashi H; Tsuji S

Department of Neurology, Brain Research Institute, Niigata University, Asahimachi Niigata, Japan.

Nature genetics (UNITED STATES) Feb 1998, 18 (2) p111-7, ISSN 1061-4036 Journal Code: 9216904

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

To elucidate the molecular mechanisms whereby expanded polyglutamine stretches elicit a gain of toxic function, we expressed full-length and truncated DRPLA (dentatorubral-pallidoluysian atrophy) cDNAs with or without expanded CAG repeats in COS-7 cells. We found that truncated DRPLA proteins containing an expanded polyglutamine stretch form filamentous peri- and intranuclear aggregates and undergo **apoptosis**. The apoptotic cell death was partially suppressed by the transglutaminase inhibitors cystamine and monodansyl cadaverine (but not **putrescine**), suggesting involvement of a transglutaminase reaction and providing a potential basis for the development of therapeutic measures for CAG-repeat expansion diseases.

21/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09674057 98102598 PMID: 9439480

Direct inhibitory effect of uremic toxins and polyamines on proliferation of VERO culture cells.

Stabellini G; Mariani G; Pezzetti F; Calastrini C

Istituto di Istologia ed Embriologia Generale, Universita di Ferrara, Italy.

Experimental and molecular pathology (UNITED STATES) 1997, 64 (3) p147-55, ISSN 0014-4800 Journal Code: 0370711

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The dialysate fluid of uremic patients exhibits, in vitro, an inhibitory effect on cell growth, owing to urea, guanidino compounds, and substances named middle molecules. The polyamines are compounds which exhibit high levels in biological fluids during either normal development or disease such as psoriasis, uremia, and tumors. Dialysate and middle molecules show toxicity and degeneration of the organotype cultures, whereas the free polyamines and nonrecirculated dialysate do not have any toxic effect. The aim of this study is to analyze the effects of polyamines, nonrecirculated dialysate, and middle molecules of uremic patients in periodic hemodialysis on cultured VERO (fibroblast-like cells) growth. These cells show an inhibition of growth in middle molecules or 2×10^{-4} M **putrescine** and a stimulation with nonrecirculated dialysate and 2×10^{-8} M **putrescine**. The effect is different because the cultures with middle molecules begin growth again after 24 hr, whereas in the presence of 2×10^{-4} M **putrescine** no further growth is observed. Cells maintained in middle molecules + 2×10^{-8} M **putrescine** show an irreversible degeneration, attesting a toxic effect due to the low molarities of **putrescine**. The electron microscopy shows alteration of cytoplasmic, mitochondrial, and nuclear membranes, but no chromatin fragmentation with either middle molecules or 2×10^{-4} M **putrescine**: this suggests that the cells do not die of **apoptosis**. In conclusion, during uremia the polyamines could cause toxic effects, even at low concentrations, on cells stressed by other toxic stimuli.

21/3,AB/36 (Item 36 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09627964 98063022 PMID: 9398458

Neurotoxicity of polyamines and pharmacological neuroprotection in cultures of rat cerebellar granule cells.

Sparapani M; Dall'Olio R; Gandolfi O; Ciani E; Contestabile A

Department of Biology, University of Bologna, Italy.

Experimental neurology (UNITED STATES) Nov 1997, 148 (1) p157-66,

ISSN 0014-4886 Journal Code: 0370712

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We have studied in a well-characterized in vitro neuronal system, cultures of cerebellar granule cells, the toxicity of polyamines endogenously present in the brain: spermine, spermidine, and **putrescine**. Twenty-four-hour exposure of mature (8 days in vitro) cultures to 1-500 microM spermine resulted in a dose-dependent death of granule cells, with the half-maximal effect being reached below 50 microM concentration. **Putrescine** was moderately toxic but only at 500 microM concentration. Spermidine was tested at 50 and 100 microM concentration and its toxicity was evaluated to be about 50% that of spermine. Neuronal death caused by spermine occurred, at least in part, by **apoptosis**. Spermine toxicity was completely prevented by competitive (CGP 39551) and noncompetitive (MK-801) antagonists of the NMDA receptor, but was unaffected by a non-NMDA antagonist (NBQX) or by antagonists of the polyamine site present on the NMDA receptor complex, such as ifenprodil. A partial protection from spermine toxicity was obtained through the simultaneous presence of free radical scavengers or through inhibition of the free radical-generating enzyme nitric oxide synthase, known to be partially effective against direct glutamate toxicity. The link between spermine toxicity and glutamate was further strengthened by the fact that, under culture conditions in which glutamate toxicity was ineffective or much reduced, spermine toxicity was absent or very much decreased. Exposure to spermine was accompanied by a progressive accumulation of glutamate in the medium of granule cell cultures. This was attributed to glutamate leaking out from dying or dead cells and was substantially prevented by the simultaneous presence of MK-801 or CGP 39551. The present results demonstrate that polyamines are toxic to granule cells in culture and that this toxicity is mediated through the NMDA receptor by interaction of exogenously added polyamines with endogenous glutamate released by neurons in the medium. The involvement of brain polyamines, in particular spermine and spermidine, in excitotoxic neuronal death is strongly supported by our present results.

21/3,AB/37 (Item 37 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09625023 98055602 PMID: 9395224

Dysregulation of ornithine decarboxylase activity, **apoptosis** and Bcl-2 oncoprotein in Syrian hamster embryo cells stage-exposed to di(2-ethylhexyl)phthalate and tetradecanoylphorbol acetate.

Dhalluin S; Gate L; Vasseur P; Tapiero H; Nguyen-Ba G

Laboratory of Cellular and Molecular Pharmacology, URA CNRS 1218, Faculty of Pharmacy, Chateney-Malabry, France.

Carcinogenesis (ENGLAND) Nov 1997, 18 (11) p2217-23, ISSN 0143-3334
Journal Code: 8008055

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Perturbations of cell proliferation and death are considered as essential events in the process of carcinogenesis. Thus, two parameters, ornithine decarboxylase (ODC), an enzyme closely related to cell proliferation and transformation, and apoptotic phenomenon are profoundly modified. Using Syrian hamster embryo (SHE) cells, we have examined in the framework of two-stage carcinogenesis (initiation-promotion) the effects of a non-genotoxic [diethylhexylphthalate (DEHP)] or genotoxic [benzo[a]pyrene (BaP)] carcinogen or a non-carcinogenic compound [phthalic anhydride (AP)] on these parameters. Immunoreactive Bcl-2 and Bcl-xL proteins were also investigated following two-stage exposures. Whereas exposures to BaP, DEHP or AP alone did not provoke any modification of ODC activity, the phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA), strongly increased it. Using two-stage exposure protocol (xenobiotics first, then replacement by TPA-promoter), the ODC activity was higher than that obtained with TPA alone. This superinduction of ODC activity was observed only with the carcinogenic compounds DEHP and BaP. Following the same exposure protocol, spontaneous cellular **apoptosis** was decreased. Furthermore, Bcl-2 oncoprotein was also upregulated approximately 8- and 11-fold for BaP and DEHP respectively; meanwhile Bcl-xL protein rate did not change. The non-carcinogenic compound AP slightly inhibited spontaneous SHE cell death without ODC superinduction. Exogenous polyamines, **putrescine**, spermidine and spermine diluted in the medium did not inhibit spontaneous **apoptosis**. Although inhibition of **apoptosis** was not specific of carcinogenic compound, both superinduction of ODC activity and inhibition of **apoptosis** via Bcl-2 upregulation, may cooperate during early stages of the carcinogenic process.

21/3,AB/38 (Item 38 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09441120 97330994 PMID: 9185519

The role of transglutaminase in the rat subtotal nephrectomy model of renal fibrosis.

Johnson T S; Griffin M; Thomas G L; Skill J; Cox A; Yang B; Nicholas B; Birckbichler P J; Muchaneta-Kubara C; Meguid El Nahas A
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Journal of clinical investigation (UNITED STATES) Jun 15 1997, 99 (12) p2950-60, ISSN 0021-9738 Journal Code: 7802877

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Tissue transglutaminase is a calcium-dependent enzyme that catalyzes the cross-linking of polypeptide chains, including those of extracellular matrix (ECM) proteins, through the formation of epsilon-(gamma-glutamyl) lysine bonds. This crosslinking leads to the formation of protein polymers that are highly resistant to degradation. As a consequence, the enzyme has been implicated in the deposition of ECM protein in fibrotic diseases such as pulmonary fibrosis and atherosclerosis. In this study, we have investigated the involvement of tissue transglutaminase in the development of kidney fibrosis in adult male Wistar rats submitted to subtotal nephrectomy (SNx). Groups of six rats were killed on days 7, 30, 90, and 120 after SNx. As previously described, these rats developed progressive glomerulosclerosis and tubulo-interstitial fibrosis. The tissue level of epsilon-(gamma-glutamyl) lysine cross-link (as determined by exhaustive proteolytic digestion followed by cation exchange chromatography) increased from 3.47 +/- 0.94 (mean +/- SEM) in controls to 13.24 +/- 1.43 nmol/g protein 90 d after SNx, $P \leq 0.01$. Levels of epsilon-(gamma-glutamyl) lysine cross-link correlated well with the renal fibrosis score throughout the 120 observation days ($r = 0.78$, $P \leq 0.01$). Tissue homogenates showed no significant change in overall transglutaminase activity (14C **putrescine** incorporation assay) unless adjusted for the loss of

viable tubule cells, when an increase from 5.77+/-0.35 to 13.93+/-4.21 U/mg DNA in cytosolic tissue transglutaminase activity was seen. This increase was supported by Western blot analysis, showing a parallel increase in renal tissue transglutaminase content. Immunohistochemistry demonstrated that this large increase in epsilon-(gamma-glutamyl) lysine cross-link and tissue transglutaminase took place predominantly in the cytoplasm of tubular cells, while immunofluorescence also showed low levels of the epsilon-(gamma-glutamyl) lysine cross-link in the extracellular renal interstitial space. The number of cells showing increases in tissue transglutaminase and its cross-link product, epsilon-(gamma-glutamyl) lysine appeared greater than those showing signs of typical **apoptosis** as determined by in situ end-labeling. This observed association between tissue transglutaminase, epsilon-(gamma-glutamyl) lysine cross-link, and renal tubulointerstitial scarring in rats submitted to SNx suggests that tissue transglutaminase may play an important role in the development of experimental renal fibrosis and the associated loss of tubule integrity.

21/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09388149 97270327 PMID: 9125410

Polyamines prevent apoptotic cell death in cultured cerebellar granule neurons.

Harada J; Sugimoto M
Neuroscience Research Laboratories, Sankyo Co. Ltd., Shinagawa-ku, Tokyo, Japan. jyunha@shina.sankyo.co.jp
Brain research (NETHERLANDS) Apr 11 1997, 753 (2) p251-9, ISSN 0006-8993 Journal Code: 0045503
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Polyamines play critical roles during the development of brain neurons. In the present study we examined the effects of polyamines on neuronal apoptotic death. Rat cerebellar granule neurons were cultured in the presence of a depolarizing concentration of KCl (25 mM) in the medium. Apoptotic neuronal death was induced by changing the medium to that containing 5.6 mM KCl without serum. Spermine as well as spermidine and **putrescine** prevented cell death in a concentration-dependent manner with the order of potency being spermine > spermidine > **putrescine**. The effect of spermine was partially blocked by several NMDA-type glutamate receptor antagonists including (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cy clohepten-5,10-imine (MK-801). MK-801-sensitive neuroprotection by spermine depended on cell density. Activation of CPP32 (caspase-3/Yama/apopain)-like proteolytic activity, a key mediator of **apoptosis**, precedes neuronal death, and polyamines prevented an increase in this activity. These results demonstrate that polyamines protect neurons from apoptotic cell death through both NMDA receptor-dependent and -independent mechanisms, acting upstream from the activation of CPP32-like protease(s).

21/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09274957 97177271 PMID: 9024798

Loss of intracellular **putrescine** pool-size regulation induces **apoptosis**.

Xie X; Tome M E; Gerner E W
Department of Radiation Oncology/Cancer Biology Division, Arizona Health Sciences Center, The University of Arizona, Tucson 85724, USA.
Experimental cell research (UNITED STATES) Feb 1 1997, 230 (2) p386-92, ISSN 0014-4827 Journal Code: 0373226
Contract/Grant No.: CA-23074; CA; NCI; CA-30052; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Synthesis and uptake are two important regulated mechanisms by which eukaryotic cells maintain polyamine levels. The role that loss of synthesis and/or uptake regulation plays in mediating **putrescine** toxicity was investigated by comparing toxicity in an ornithine decarboxylase (ODC)-deficient Chinese hamster ovary cell line (C55.7) with a functional **putrescine** transport system and an ODC-overproducing rat hepatoma cell line (DH23b), which are transport regulation deficient. When C55.7 cells were transfected with either mouse ODC (M) or trypanosome ODC (Tb), intracellular **putrescine** content increased slightly in C55.7(Tb-ODC), compared to C55.7(M-ODC), due to the lack of response of Tb-ODC to polyamine regulation. The increase in **putrescine** content resulting from loss of ODC regulation had no impact on cell growth and viability. When the feedback repression of polyamine uptake was blocked with cycloheximide, C55.7 cells transfected with either ODC construct accumulated very high levels of **putrescine** from the medium, and underwent **apoptosis** in a **putrescine** dose-dependent manner. A similar correlation of deregulated **putrescine** uptake and increased apoptotic cells was observed in DH23b cells. These data demonstrate that loss of feedback regulation on the polyamine transport system, but not ODC activity, is sufficient to induce **apoptosis**. Thus, downregulation of the transport system is necessary to prevent accumulation of cytotoxic **putrescine** levels in rodent cells.

21/3,AB/41 (Item 41 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08807645 96172202 PMID: 8583963

Polyamine involvement in the cell cycle, **apoptosis**, and autoimmunity.

Brooks W H

Department of Biochemistry, Medical College of Wisconsin 53226, USA.

Medical hypotheses (ENGLAND) May 1995, 44 (5) p331-8, ISSN 0306-9877 Journal Code: 7505668

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The polyamines: **putrescine**, spermidine and spermine, are ubiquitous polycations which have numerous, unique interactions in eukaryotic cells. Polyamines are essential for cell growth, with the bulk of polyamine expression co-ordinated with the cell cycle. The length, charge, and charge distribution of polyamines permit them to interact with large anionic molecules such as DNA, RNA, and phospholipids. Here, a mechanism is proposed whereby cell cycle expression of polyamines at the start of S phase leads to disruption of transcription and splicing, giving priority to DNA and histone synthesis. Inappropriate initiation of this process in non-viable cells leads to **apoptosis** and may be an underlying cause of autoimmunity.

21/3,AB/42 (Item 42 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08727311 96067584 PMID: 7487924

Induction of **apoptosis** by excessive polyamine accumulation in ornithine decarboxylase-overproducing L1210 cells.

Poulin R; Pelletier G; Pegg A E

Department of Physiology, Laval University Medical Research Center, Ste. Foy, Quebec, Canada.

Biochemical journal (ENGLAND) Nov 1 1995, 311 (Pt 3) p723-7, ISSN 0264-6021 Journal Code: 2984726R
Contract/Grant No.: GM-26290; GM; NIGMS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Deregulation of polyamine transport in L1210 cells overexpressing ornithine decarboxylase leads to a lethal accumulation of spermidine. We now provide evidence that over-accumulation of natural and synthetic polyamines, but not **putrescine**, rapidly induces **apoptosis**, as shown by hypercondensation of peripheral chromatin and internucleosomal cleavage, followed by nuclear fragmentation. Polyamine oxidation is not responsible for the **apoptosis** observed. Thus, abnormally high polyamine pools could be an important physiological trigger of **apoptosis**.

21/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08719313 96083793 PMID: 7593241

Regulation of **apoptosis** of interleukin 2-dependent mouse T-cell line by protein tyrosine phosphorylation and polyamines.

Min A; Hasuma T; Yano Y; Matsui-Yuasa I; Otani S

Department of Biochemistry, Osaka City University Medical School, Japan.

Journal of cellular physiology (UNITED STATES) Dec 1995, 165 (3) p615-23, ISSN 0021-9541 Journal Code: 0050222

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We examined the effect of inhibitors of tyrosine kinase and tyrosine phosphatase on DNA fragmentation, protein tyrosine phosphorylation, and polyamine metabolism in the murine T-cell line CTLL-2. When cells were exposed to herbimycin A, a specific inhibitor of tyrosine kinase (Uehara et al., 1989, Biochem. Biophys. Res. Commun., 163:803-809), in the presence of interleukin 2 (IL-2), DNA was degraded into oligonucleosomal fragments in a dose-dependent fashion. Genistein, another inhibitor of tyrosine kinase (Akiyama et al., 1987, J. Biol. Chem., 262:5592-5596), had similar effects. Exposure of CTLL-2 cells to vanadate, a tyrosine phosphatase inhibitor, blocked with the DNA fragmentation induced by herbimycin A. Tyrosine phosphorylation of 55 Kd protein was inhibited by herbimycin A, and the inhibition was reduced by vanadate. Ornithine decarboxylase (ODC) activity decreased rapidly after herbimycin A was added to CTLL-2 cell cultures, while vanadate increased ODC activity. The exogenous addition of **putrescine** or spermine, but not that of spermidine, attenuated herbimycin A-induced DNA fragmentation. These findings suggest that phosphorylation of tyrosine residues of 55 Kd protein prevents DNA fragmentation and that polyamines are involved in regulation of **apoptosis**.

21/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08712045 96069141 PMID: 7577467

Evaluation of the significance of polyamines and their oxidases in the aetiology of human cervical carcinoma.

Fernandez C; Sharrard R M; Talbot M; Reed B D; Monks N

Institute for Cancer Studies, University of Sheffield Medical School, UK.

British journal of cancer (SCOTLAND) Nov 1995, 72 (5) p1194-9,

ISSN 0007-0920 Journal Code: 0370635

Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The risk of cancer of the cervix is linked with sexual behaviour. Although infectious agents such as human papillomaviruses (HPVs) are implicated, these alone may be insufficient to induce the disease. We have investigated the potential role of oxidation products of the polyamines spermine and spermidine and the diamine **putrescine** in seminal plasma (SP) as co-factors in the development of cervical cancer. These amines are oxidised by polyamine oxidase (PAO) and diamine oxidase (DAO) to generate oxygen radicals and hydrogen peroxide, reactive aldehydes and acrolein, which are likely to exert local mutagenic, cytotoxic and immunosuppressive effects in vivo. Using a chemiluminescence assay, we determined the levels of these amines in 187 samples of SP. Spermine plus spermidine, as substrates for PAO, were present in a range equivalent to 0-4.8 mg ml⁻¹ spermine. **Putrescine**, as a substrate for DAO, was detectable in only 4 of 40 samples assayed (range 0-168 micrograms ml⁻¹) and constitutes a minor component of the oxidisable content of SP. Cervical mucus (126 samples) was assayed for the presence of PAO and DAO. Both enzymes were present in 14.3% of the samples, PAO only in 21.4%, DAO only in 15.1% and neither enzyme in 49.2%. PAO levels ranged from 0 to 0.828 pmol peroxide generated min⁻¹ mg⁻¹ mucus and DAO levels ranged from 0 to 7.0 pmol peroxide generated min⁻¹ mg⁻¹ mucus. These results suggest that sexual activity in the absence of physical barrier contraception may lead to the generation of mutagenic and immunosuppressive polyamine oxidation products within the female genital tract. We thus propose that women with high levels of PAO and/or DAO in their cervical mucus may be at increased risk of cervical cancer, especially if the male partner's SP shows high polyamine levels. HPV infection may synergise with the effects of polyamine oxidation by suppressing **apoptosis** in keratinocytes carrying potentially oncogenic mutations, leading to the survival and proliferation of transformed cells in the cervix.

21/3,AB/45 (Item 45 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

07968665 94107975 PMID: 8280812
TGF-beta 1 inhibits polyamine biosynthesis in K 562 leukemic cells.
Motyl T; Kasterka M; Grzelkowska K; Blachowski S; Sysa P
Department of Animal Physiology, Warsaw Agricultural University, Poland.
Annals of hematology (GERMANY) Dec 1993, 67 (6) p285-8, ISSN
0939-5555 Journal Code: 9107334
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The present study proved that TGF-beta 1 significantly inhibited the growth of K 562 cells. The drop in cell numbers after 24 h incubation with increasing concentrations of TGF-beta 1 (0.01, 0.1, 1.0, 10.0 ng/ml) was accompanied by significant suppression of the activity of two key enzymes of polyamine biosynthesis: ornithine decarboxylase (ODC) and S-adenosylmethionine decarboxylase (SAMDC). In contrast to ODC and SAMDC activity, TGF-beta 1 did not significantly affect the absolute concentration of spermidine and spermine in K 562 cells. We suppose that the lack of an evident drop in concentration of spermidine and spermine in spite of a significant decrease in ODC and SAMDC activity in K 562 cells exposed to TGF-beta 1 resulted from the uptake of polyamines from the extracellular space.

21/3,AB/46 (Item 46 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

Spermine prevents endonuclease activation and **apoptosis** in thymocytes.

Brune B; Hartzell P; Nicotera P; Orrenius S

Department of Toxicology, Karolinska Institutet, Stockholm, Sweden.

Experimental cell research (UNITED STATES) Aug 1991, 195 (2) p323-9,

ISSN 0014-4827 Journal Code: 0373226

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Glucocorticoid hormones, Ca^{2+} ionophores, and some toxic chemicals activate a suicide process in thymocytes, known as **apoptosis** or programmed cell death. A crucial event in **apoptosis** is the activation of a Ca^{2+} - and Mg^{2+} -dependent endonuclease that promotes extensive DNA fragmentation. In this study, we investigated the effect of various polyamines on endonuclease activation leading to thymocyte **apoptosis**. We found that both glucocorticoid- and Ca^{2+} ionophore-induced DNA fragmentation and **apoptosis** were prevented by spermine. Other polyamines such as **putrescine** or spermidine had moderate or no effect. Moreover, spermine, and to a lesser extent spermidine, but not **putrescine**, prevented endonuclease activation in permeabilized liver nuclei incubated in the presence of Ca^{2+} and Mg^{2+} , indicating that spermine efficiency in blocking DNA fragmentation was related to the interaction of this polyamine with the endonuclease or its substrate, DNA. Experiments with the fluorescent dye, ethidium bromide, and a purified preparation of liver endonuclease revealed that the protective effect of spermine on DNA fragmentation was related to its ability to modify the chromatin arrangement. Thymocytes incubated with methyl glyoxal bis(guanyldrazone) to deplete intracellular spermine exhibited spontaneous DNA fragmentation, which suggests that modulation of the intracellular polyamine content and regulation of chromatin structure may play a critical role in the early phases of **apoptosis**. Finally, these results demonstrate that inhibition of DNA fragmentation also prevents the onset of **apoptosis**, directly linking endonuclease activation and cell death.

21/3,AB/47 (Item 1 from file: 5)

DIALOG(R)File 5:BIOSIS Previews(R)

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13741438 BIOSIS NO.: 200200370259

Involvement of tyrosine phosphorylation and intracellular sulphydryl groups in 1'-acetoxychavicol acetate-induced cell death of Ehrlich ascites tumor cells.

AUTHOR: Moffatt Jerry(a); Kojima Akiko(a); Matsui-Yuasa Isao(a)

AUTHOR ADDRESS: (a)Food and Health Sciences, Osaka City University, 3-3-138

Sugimoto cho, Sumiyoshi-ku, Osaka, 558-8585**Japan

JOURNAL: FASEB Journal 16 (5):pA1001 March 22, 2002

MEDIUM: print

CONFERENCE/MEETING: Annual Meeting of Professional Research Scientists on

Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002

ISSN: 0892-6638

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: 1'-acetoxychavicol acetate (ACA) is a natural product obtained from the rhizomes and seeds of *Languas Galanga* and exhibits broad range anticarcinogenic activity. We have shown that ACA induced loss of viability in Ehrlich ascites tumor cells whose morphological features cells indicated apoptotic characteristics such as membrane blebbing and condensed nucleus. Further ACA suppressed and induced ornithine decarboxylase (ODC) and spermidine/spermine N1-acetyltransferase (SSAT) activities respectively both dose-and

time-dependently. At 4 h levels of intracellular polyamines, **putrescine**, spermidine and spermine were markedly decreased, particularly that of **putrescine**. Here, in vitro, the antitumor efficacy of ACA was made by investigating its effects on tyrosine phosphorylation, MAPK and JNK/SAPK activities and intracellular sulfhydryl groups and cell cycle. Methodology: Western blotting for tyrosine phosphorylated proteins and kinase activities, DNTB oxidation of SH groups for intracellular sulfhydryl groups and laser scanning cytometer for cell cycle. Results: ACA induced dose- and time- dependent phosphorylation of tyrosine phosphorylation of 27 kDa and 70 kDa proteins and reduced intracellular sulfhydryl groups and caused cell cycle arrest. N-acetyl cysteine co-incubation abolished tyrosine phosphorylation of the 27 kDa protein. While ACA decreased p42/44 MAPK activity it had a modest stimulatory effect on JNK/SAPK activity. Conclusion: These results reveal that changes in MAPK and JNK activities, a pro-oxidant activity and its effect on tyrosine phosphorylation, at least on a 27 kDa protein and cell cycle arrest are involved in ACA- induced **apoptosis**.

2002

21/3,AB/48 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13741402 BIOSIS NO.: 200200370223

Toxic level of selenium induces hepatic injury and biliary ductule **apoptosis** in rats.

AUTHOR: Yang Feili Lo(a); Chen Yu-Shin(a); Weaver Cyprian V

AUTHOR ADDRESS: (a)Department of Nutrition and Food Sciences, Fu Jen Catholic University, 510 Chungcheng Rd., Shinjuang, Taipei Shein, 24205** Taiwan

JOURNAL: FASEB Journal 16 (5):pA994 March 22, 2002

MEDIUM: print

CONFERENCE/MEETING: Annual Meeting of Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002

ISSN: 0892-6638

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Excessive Se consumption was reported to damage liver of rats.

This study was designed to assess the changes of several biochemical indices of liver function and pathological characteristics during the time course of developing Se liver toxicity. Seventy-two weanling male Wistar rats were randomly assigned to receive AIN 93G-based diets modified to provide 2 mg of folate, 2.5 g of choline bitartrate and either 0.1 mg or 5 mg of Se per kg of diet for 2, 4, 6 or 8 wks. Excessive Se feeding rapidly increased liver Se level 22 folds to that of control rats at week 2. Toxic level of Se feeding elevated plasma prothrombin time, SGOT, liver **putrescine** level and SPD/SPM ratio and lowered serum albumin and liver spermine levels during the same period of treatment. Hematoxylin and eosin stained liver sections of rats fed excessive Se revealed vacuolization of hepatocytes around portal vein, initial fatty liver changes, regional necrosis as well as thickening of smooth muscle layer and proliferation of biliary ductules. TUNEL staining of liver sections showed **apoptosis** mainly in the epithelial cells surrounding biliary ductule wall. Our study suggests that toxic level of Se feeding altered Se status and impaired liver functions of rats within 2 wks. Specific localization of **apoptosis** within biliary ductules requires further investigation to determine the reason for biliary epithelia as target for Se induced programmed cell death.

2002

21/3,AB/49 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13564671 BIOSIS NO.: 200200193492

Effects of 17beta-estradiol administration on **apoptosis** and polyamine content in AGS cell line.

AUTHOR: Pricci Maria; Linsalata Michele; Russo Francesco; Messa Caterina; Amati Luigi; Caradonna Luigi; Jirillo Emilio; Di Leo Alfredo(a)

AUTHOR ADDRESS: (a)Biochemistry Laboratory, I.R.C.C.S. "Saverio de Bellis" Scientific Institute for Digestive Diseases, Via della Resistenza, I-70013, Castellana Grotte, BA**Italy E-Mail: irccsbiochimica@libero.it

JOURNAL: Anticancer Research 21 (5):p3215-3220 September-October, 2001

MEDIUM: print

ISSN: 0250-7005

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: Estrogens and polyamines seem to play an important role not only in cell growth and differentiation, but also in programmed cell death. The aim of the present study was to investigate the effects of 17beta-estradiol supplementation on **apoptosis** as well as on the polyamine content of an ER- positive human gastric cancer cell line (AGS). Materials and Methods: **Apoptosis** was investigated by evaluating DNA fragmentation, using enzyme immunoassay and agarose gel electrophoresis and the phosphatidylserine exposure by flow cytometry analysis. Polyamine levels were evaluated by HPLC. Results: 17beta-estradiol gave rise to a marked pro-apoptotic effect at concentrations of 16 muM or higher compared to the control. Moreover; the hormone significantly reduced the contents of polyamines compared to control cells. The apoptotic effect of 17beta-estradiol was partially counteracted by exogenous spermine administration. Conclusion: 17beta-estradiol administration induces **apoptosis** in AGS cells. Further, an increase in cell sensitivity to **apoptosis** due to a decline in the polyamine content may be suggested.

2001

21/3,AB/50 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13539708 BIOSIS NO.: 200200168529

Glucocorticoids and polyamine inhibitors synergize to kill human leukemic CEM cells.

AUTHOR: Miller Aaron L; Johnson Betty H; Medh Rheem D; Townsend Courtney M; Thompson E Brad(a)

AUTHOR ADDRESS: (a)Department of Human Biological Chemistry and Genetics, University of Texas Medical Branch, Galveston, TX, 77555-0645**USA
E-Mail: bthomposo@utmb.edu

JOURNAL: Neoplasia (New York) 4 (1):p68-81 January-February, 2002

MEDIUM: print

ISSN: 1522-8002

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Glucocorticoids are well-known apoptotic agents in certain classes of lymphoid cell malignancies. Reduction of intracellular polyamine levels by use of inhibitors that block polyamine synthesis

slows or inhibits growth of many cells in vitro. Several such inhibitors have shown efficacy in clinical trials, though the toxicity of some compounds has limited their usefulness. We have tested the effects of combinations of the glucocorticoid dexamethasone (Dex) and two polyamine inhibitors, difluoromethylornithine (DFMO) and methyl glyoxal bis guanylylhydrazone (MGBG), on the clonal line of human acute lymphoblastic leukemia cells, CEM-C7-14. Dex alone kills these cells, though only after a delay of at least 24 hours. We also evaluated a partially glucocorticoid-resistant c-Myc-expressing CEM-C7-14 clone. We show that Dex downregulates ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine synthesis. Pretreatment with the ODC inhibitor DFMO, followed by addition of Dex, enhances steroid-evoked kill slightly. The combination of pretreatment with sublethal concentrations of both DFMO and the inhibitor of S-adenosylmethionine decarboxylase, MGBG, followed by addition of Dex, results in strong synergistic cell kill. Both the rapidity and extent of cell kill are enhanced compared to the effects of Dex alone. These results suggest that use of such combinations in vivo may result in **apoptosis** of malignant cells with lower overall toxicity.

2002

21/3,AB/51 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
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13368933 BIOSIS NO.: 200100576082

Induction of **apoptosis** in human gastric cancer cell lines by the polyamine synthesis inhibitor, methylglyoxal bis(cyclopentylamidino)hydrazone (MGBCP).

AUTHOR: Nakashima S; Hibasami H(a); Tamaki S; Toyota N; Taguchi Y; Yamaguchi M; Gabazza E C; Ikoma J; Kaito M; Imoto I; Nakashima K; Adachi Y

AUTHOR ADDRESS: (a)Faculty of Medicine, Department of Medical Sciences, Mie University, 2-174 Edobashi, Tsu-city, Mie, 514-8507**Japan

JOURNAL: Biogenic Amines 16 (4-5):p327-342 2001

MEDIUM: print

ISSN: 0168-8561

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Polyamines are important intracellular mediators of cell proliferation in cancer cells. In this study, we evaluated whether methylglyoxal bis(cyclopentylamidino)hydrazone (MGBCP), a polyamine synthesis inhibitor, induces **apoptosis** and inhibits growth in gastric cancer cell lines (MKN-1, MKN-28, MKN-45). For comparison, the same experiment was carried out in a normal rat gastric epithelial cell line (RGM-1). The growth of gastric cancer cell lines was dose-dependently inhibited by MGBCP. Almost all the cells became apoptotic when they were cultured in the presence of 40 μ M MGBCP for 5 days. Very high concentration (200 μ M) of MGBCP was needed to completely inhibit the proliferation of RGM-1 cells. The cellular concentrations of the polyamines, spermidine and spermine were significantly reduced (50%) when the gastric cancer cells were cultured in the presence of MGBCP (80 μ M) for 5 days. **Putrescine** remained unchanged. The reductions of both spermidine and spermine were mild in RGM-1 cells. DNA fragmentation and TUNEL studies demonstrated the occurrence of **apoptosis** in gastric cancer cell lines but not in RGM-1 cells. The results of this study suggest the potential usefulness of MGBCP as an anti-cancer agent in gastric cancer.

2001

21/3,AB/52 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13361045 BIOSIS NO.: 200100568194
Selective accumulation of **putrescine** in ornithine decarboxylase
overproducing cells induces caspase dependent **apoptosis**.
AUTHOR: Erez O(a); Kahana C(a)
AUTHOR ADDRESS: (a)Department of Molecular Genetics, Weizmann Institute of
Science, Rehovot**Israel
JOURNAL: Amino Acids (Vienna) 21 (1):p64 2001
MEDIUM: print
CONFERENCE/MEETING: 7th International Congress on Amino Acids and Proteins
Vienna, Austria August 06-10, 2001
ISSN: 0939-4451
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

21/3,AB/53 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13329244 BIOSIS NO.: 200100536393
Translocation of tissue transglutaminase from cytoplasm to nucleus plays a
role in ethanol-induced **apoptosis** in rat hepatocytes.
AUTHOR: Song Liang-Wen(a); Wu Jian(a); Kojima Soichi; Zern Mark A
AUTHOR ADDRESS: (a)UC Davis Medical Center, Sacramento, CA**USA
JOURNAL: Hepatology 34 (4 Pt. 2):p274A October, 2001
MEDIUM: print
CONFERENCE/MEETING: 52nd Annual Meeting and Postgraduate Courses of the
American Association for the Study of Liver Diseases Dallas, Texas, USA
November 09-13, 2001
ISSN: 0270-9139
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

21/3,AB/54 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13274863 BIOSIS NO.: 200100482012
Effects of tissue transglutaminase on retinoic acid-induced cellular
differentiation and protection against **apoptosis**.
AUTHOR: Antonyak Marc A; Singh Ugra S; Lee David A; Boehm Jason E; Combs
Carolyn; Zgola Marsha M; Page Rodney L; Cerione Richard A(a)
AUTHOR ADDRESS: (a)Dept. of Molecular Medicine, VMC, Cornell University,
Ithaca, NY, 14853-6401: rac1@cornell.edu**USA
JOURNAL: Journal of Biological Chemistry 276 (36):p33582-33587 September
7, 2001
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Retinoic acid (RA) and its various synthetic analogs affect mammalian cell growth, differentiation, and **apoptosis**. Whereas treatment of the human leukemia cell line HL60 with RA results in cellular differentiation, addition of the synthetic retinoid, N-(4-hydroxyphenyl) retinamide (HPR), induces HL60 cells to undergo **apoptosis**. Moreover, pretreatment of HL60 cells as well as other cell lines (i.e. NIH3T3 cells) with RA blocks HPR-induced cell death. In attempting to discover the underlying biochemical activities that might account for these cellular effects, we found that monodansylcadaverine (MDC), which binds to the enzyme (transamidase) active site of tissue transglutaminase (TGase), eliminated RA protection against cell death and in fact caused RA to become an apoptotic factor, suggesting that the ability of RA to protect against **apoptosis** is linked to the expression of active TGase. Furthermore, it was determined that expression of exogenous TGase in cells exhibited enhanced GTP binding and transamidation activities and mimicked the survival advantage imparted by RA. We tested whether the ability of this dual function enzyme to limit HPR-mediated **apoptosis** was a result of the ability of TGase to bind GTP and/or catalyze transamidation and found that GTP binding was sufficient for the protective effect. Moreover, excessive transamidation activity did not appear to be detrimental to cell viability. These findings, taken together with observations that the TGase is frequently up-regulated by environmental stresses, suggest that TGase may function to ensure cell survival under conditions of differentiation and cell stress.

2001

21/3,AB/55 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13190750 BIOSIS NO.: 200100397899

Uremic toxins and polyamines: Effects on proliferation of vero cells and **apoptosis** process.

AUTHOR: Bedani P L(a); Mariani G; Pezzetti F; Bergami M(a); Pellati A; Calastrini C; Gilli P(a); Stabellini G

AUTHOR ADDRESS: (a)Div. Nephrol., S. Anna Hospital, Ferrara**Italy

JOURNAL: Nephrology Dialysis Transplantation 16 (6):pA173 June, 2001

MEDIUM: print

CONFERENCE/MEETING: Annual Congress of the European Renal Association and the European Dialysis and Transplant Association Vienna, Austria June 24-27, 2001

ISSN: 0931-0509

RECORD TYPE: Citation

LANGUAGE: English

SUMMARY LANGUAGE: English

2001

21/3,AB/56 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12711785 BIOSIS NO.: 200000465287

2-deoxy-D-ribose-induced **apoptosis** in HL-60 cells is associated with the cell cycle progression by spermidine.

AUTHOR: Monti Maria Giuseppina(a); Ghiaroni Stefania; Barbieri Daniela; Franceschi Claudio; Marverti Gaetano; Moruzzi Maria Stella

AUTHOR ADDRESS: (a)Dipartimento di Scienze Biomediche, Sezione di Chimica Biologica, Via Campi 287, 41100, Modena**Italy

JOURNAL: Biochemical and Biophysical Research Communications 257 (2):p

460-465 April 13, 1999
MEDIUM: print
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The presence of polyamines is required for the apoptotic program triggered by 2-deoxy-D-ribose (dRib) in HL-60 cells, but their oxidative metabolites does not appear to be involved in the oxidative stress caused by the sugar. The present study points to a relationship between spermidine-induced G1 to S phase transition and the onset of dRib-induced **apoptosis**. Conversely, the G1 block induced by alpha-difluoromethylornithine (DFMO) is associated with a protective effect against dRib-induced cell suicide. Replenishment of the intracellular spermidine pool by exogenous **putrescine** and spermidine induces cell cycle progression and restores apoptotic levels. The present data indicate that the induction of cell cycle progression by spermidine is a condition facilitating the activation of the apoptotic process by dRib.

1999

21/3,AB/57 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12515479 BIOSIS NO.: 200000268981
Polyamine depletion increases the susceptibility of intestinal epithelial cells to **apoptosis** via activation but not suppression of NF-kappaB activity.
AUTHOR: Li Li(a); Jaladanki Rao N(a); Bass Barbara L(a); Wang Jian-Ying(a)
AUTHOR ADDRESS: (a)Univ of Maryland, Baltimore, MD**USA
JOURNAL: Gastroenterology 118 (4 Suppl. 2 Part 2):pAGA A1129 April, 2000
MEDIUM: print.
CONFERENCE/MEETING: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA May 21-24, 2000
SPONSOR: American Gastroenterological Association
ISSN: 0016-5085
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

21/3,AB/58 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12507446 BIOSIS NO.: 200000260948
Oxidation of polyamines and brain injury.
AUTHOR: Seiler N(a)
AUTHOR ADDRESS: (a)CJF INSERM 95-05, Institut de Recherche Contre les Cancers de l'Appareil Digestif (IRCAD), 1, place de l'hôpital, 67091, Strasbourg Cedex**France
JOURNAL: Neurochemical Research 25 (4):p471-490 April, 2000
MEDIUM: print.
ISSN: 0364-3190
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Several amine oxidases are involved in the metabolism of the natural polyamines **putrescine**, spermidine, and spermine, and play a role in the regulation of intracellular concentrations, and the elimination of these amines. Since the products of the amine oxidase-catalyzed reactions - hydrogen peroxide and aminoaldehydes - are cytotoxic, oxidative degradations of the polyamines have been considered as a cause of apoptotic cell death, among other things in brain injury. Since a generally accepted, unambiguous nomenclature for amine oxidases is missing, considerable confusion exists with regard to the polyamine oxidizing enzymes. Consequently the role of the different amine oxidases in physiological and pathological processes is frequently misunderstood. In the present overview the reactions, which are catalyzed by the different polyamine-oxidizing enzymes are summarized, and their potential role in brain damage is discussed.

2000

21/3,AB/59 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12414602 BIOSIS NO.: 200000168104

Transglutaminase reactivity of human involucrin.

AUTHOR: Lambert Adam; Ekambaram Meena; Robinson Nancy; Eckert Richard L(a)

AUTHOR ADDRESS: (a)Department of Physiology/Biophysics, Case Western Reserve University School of Medicine, 2109 Adelbert Road, Rm E532, Cleveland, OH, 44106-4970**USA

JOURNAL: Skin Pharmacology and Applied Skin Physiology. 13 (1):p17-30
Jan.-Feb., 2000

ISSN: 1422-2868

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Human involucrin (hINV) is assembled into cornified structures via formation of transglutaminase (TG)-dependent interprotein epsilon-(gamma-glutamyl)lysine bonds. The hINV sequence includes 150 glutamine residues that could function as potential sites of cross-link formation. The present studies were designed to evaluate the extent to which hINV can function as a TG substrate under optimal conditions and in the absence of other substrates. Incubation of hINV with TG results in formation of 4-5 isopeptide bonds per hINV molecule. When the small amine donor **14C-putrescine** is included in the reaction, 48 Q residues are labeled. Isotope distribution and sequence analysis suggests that the **14C-putrescine**-labeled sites are located throughout the protein. Our present results show that many hINV Q residues can be utilized for cross-link formation, and that hINV can be cross-linked at very high cross-link densities. These results suggest that, in vivo, factors other than hINV structure limit the number of residues used for cross-link formation.

2000

21/3,AB/60 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11903927 BIOSIS NO.: 199900150036

The effect of cytotoxic drugs on ornithine decarboxylase activity.

AUTHOR: Mumford Gail K; Lindsay Gayle S; Wallace Heather M
AUTHOR ADDRESS: Dep. Med. Ther., Univ. Aberdeen, Aberdeen**UK
JOURNAL: Biochemical Society Transactions 26 (4):pS372 Nov., 1998
CONFERENCE/MEETING: 666th Meeting of the Biochemical Society Sheffield,
England, UK July 29-31, 1998
ISSN: 0300-5127
RECORD TYPE: Citation
LANGUAGE: English
1998

21/3,AB/61 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

11221664 BIOSIS NO.: 199800002996
Association of dexamethasone-induced **apoptosis** of G|1-arrest of human
leukemic CEM cells with polyamine deficit.
AUTHOR: Choi Sang-Hyun; Lee Jung-Ae; Chae Yang-Seok; Min Bon-Hong; Chun
Yeon-Sook; Chun Boe-Gwun(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol., Korea Univ. Coll. Med., Seoul 136-705**
South Korea
JOURNAL: Korean Journal of Physiology & Pharmacology 1 (4):p457-466 Aug.,
1997
ISSN: 1226-4512
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effects of DFMO or/and **putrescine** on the
dexamethasone-induced **apoptosis** of CEM cells were studied to
investigate the role of polyamines in anti-leukemic glucocorticoid
action. Dexamethasone-induced **apoptosis** was preceded by significant
decreases of cellular polyamine contents and **putrescine** uptake
activity. But DFMO produced decreases of **putrescine** and spermidine
contents and marked increase of **putrescine** uptake activity, but did
not induce **apoptosis**. However, dexamethasone and DFMO,
respectively, induced G|1-arrest in cell cycle and hypophosphorylation of
pRb, resulting in the increase of G|1 to S ratio and decrease of CEM cell
count. DFMO enhanced the dexamethasone-induced **apoptosis** and
G|1-arrest. On the other hand, **putrescine** little affected the
apoptotic and G|1-arresting activities of dexamethasone, but almost
suppress the effects of DFMO and also the DFMO-dependent enhancement of
dexamethasone effects. These results suggested that the
dexamethasone-induced **apoptosis** to be associated with pRb
hypophosphorylation and G|1-arrest in CEM cells might be ascribed to the
concomitant decreases of cellular polyamine contents and **putrescine**
uptake activity.

1997

21/3,AB/62 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

10331080 BIOSIS NO.: 199698785998
S-adenosylmethionine and methylation.
AUTHOR: Chiang Peter K(a); Gordon Richard K; Tal Jacov; Zeng G C; Doctor B
P; Pardhasaradhi K; McCann Peter P
AUTHOR ADDRESS: (a)Walter Reed Army Inst. Res., Washington, D.C. 20307-5100
**USA
JOURNAL: FASEB Journal 10 (4):p471-480 1996
ISSN: 0892-6638

DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: S-Adenosylmethionine (AdoMet or SAM) plays a pivotal role as a methyl donor in a myriad of biological and biochemical events. Although it has been claimed that AdoMet itself has therapeutic benefits, it remains to be established whether it can be taken up intact by cells. S-Adenosylhomocysteine (AdoHcy), formed after donation of the methyl group of AdoMet to a methyl acceptor, is then hydrolyzed to adenosine and homocysteine by AdoHcy hydrolase. This enzyme has long been a target for inhibition as its blockade can affect methylation of phospholipids, proteins, DNA, RNA, and other small molecules. Protein carboxymethylation may be involved in repair functions of aging proteins, and heat shock proteins are methylated in response to stress. Bacterial chemotaxis involves carboxymethylation and demethylation in receptor-transducer proteins, although a similar role in mammalian cells is unclear. The precise role of phospholipid methylation remains open. DNA methylation is related to mammalian gene activities, somatic inheritance, and cellular differentiation. Activation of some genes has been ascribed to the demethylation of critical mCpG loci, and silencing of some genes may be related to the methylation of specific CpG loci. Viral DNA genomes exist in cells as extrachromosomal units and are generally not methylated, although once integrated into host chromosomes, different patterns of methylation are correlated with altered paradigms of transcriptional activity. Some viral latency may be related to DNA methylation. Cellular factors have been found to interact with methylated DNA sequences. Methylation of mammalian ribosomal RNAs occurs soon after the synthesis of its 47S precursor RNA in the nucleolus before cleavage to smaller fragments. Inhibition of the methylation of rRNA affects its processing to mature 18S and 28S rRNAs. The methylation of 5'-terminal cap plays an important role in mRNA export from the nucleus, efficient translation, and protection of the integrity of mRNAs. Another important function of AdoMet is that it serves as the sole donor of an aminopropyl group that is conjugated with **putrescine** to form, first, the polyamine spermidine, and then spermine.

1996

21/3,AB/63 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

09708143 BIOSIS NO.: 199598163061
Critical role of cell polyamine content for thymocyte **apoptosis**.
AUTHOR: Desiderio M A(a); Grassilli E; Bellesia E; Limonta D; Salomoni P; Franceschi C
AUTHOR ADDRESS: (a)Inst. Gen. Pathol., CNR Cent. Res. Cell Pathol., Univ. Milano, Milano**Italy
JOURNAL: Journal of Cellular Biochemistry Supplement 0 (19B):p310 1995
CONFERENCE/MEETING: Keystone Symposium on Apoptosis (Programmed Cell Death) Tamarron, Colorado, USA March 5-11, 1995
ISSN: 0733-1959
RECORD TYPE: Citation
LANGUAGE: English
1995

21/3,AB/64 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2002 American Chemical Society. All rts. reserv.

134040092 CA: 134(4)40092y JOURNAL

Inhibition of ornithine decarboxylase by .alpha.-difluoromethylornithine induces apoptosis of HC11 mouse mammary epithelial cells
AUTHOR(S): Ploszaj, T.; Motyl, T.; Zimowska, W.; Skierski, J.; Zwierzchowski, L.
LOCATION: Department of Animal Physiology, Faculty of Veterinary Medicine, Warsaw Agricultural University, Warsaw, Pol.
JOURNAL: Amino Acids DATE: 2000 VOLUME: 19 NUMBER: 2 PAGES: 483-496
CODEN: AACIE6 ISSN: 0939-4451 LANGUAGE: English PUBLISHER: Springer-Verlag Wien

21/3,AB/65 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2002 American Chemical Society. All rts. reserv.

132320142 CA: 132(24)320142a JOURNAL
Polyamine depletion delays apoptosis of rat intestinal epithelial cells
AUTHOR(S): Ray, Ramesh M.; Viar, Mary Jane; Yuan, Qing; Johnson, L. R.
LOCATION: Department of Physiology, College of Medicine, University of Tennessee, Memphis, Memphis, TN, 38163, USA
JOURNAL: Am. J. Physiol. DATE: 2000 VOLUME: 278 NUMBER: 3, Pt. 1
PAGES: C480-C489 CODEN: AJPHAP ISSN: 0002-9513 LANGUAGE: English
PUBLISHER: American Physiological Society

21/3,AB/66 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2002 American Chemical Society. All rts. reserv.

131334887 CA: 131(25)334887p JOURNAL
Polyamine regulation of plasma membrane phospholipid flip-flop during apoptosis
AUTHOR(S): Bratton, Donna L.; Fadok, Valerie A.; Richter, Donald A.; Kailey, Jenai M.; Frasca, S. Courtney; Nakamura, Tatsuji; Henson, Peter M.
LOCATION: National Jewish Medical and Research Center, Denver, CO, 80206, USA
JOURNAL: J. Biol. Chem. DATE: 1999 VOLUME: 274 NUMBER: 40 PAGES: 28113-28120
CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

21/3,AB/67 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2002 American Chemical Society. All rts. reserv.

128152249 CA: 128(13)152249n JOURNAL
Excess putrescine accumulation inhibits the formation of modified eukaryotic initiation factor 5A (eIF-5A) and induces apoptosis
AUTHOR(S): Tome, Margaret E.; Fiser, Steven M.; Payne, Claire M.; Gerner, Eugene W.
LOCATION: Department of Radiation Oncology, Arizona Health Sciences Center, University of Arizona, Tucson, AZ, 85724, USA
JOURNAL: Biochem. J. DATE: 1997 VOLUME: 328 NUMBER: 3 PAGES: 847-854
CODEN: BIJOAK ISSN: 0264-6021 LANGUAGE: English PUBLISHER: Portland Press Ltd.

21/3,AB/68 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2002 American Chemical Society. All rts. reserv.

127119855 CA: 127(9)119855p DISSERTATION
Cellular and biochemical mechanisms of intracellular putrescine pool regulation (ornithine decarboxylase, antizyme, apoptosis, polyamines,

export, diamines)

AUTHOR(S): Xie, Xiaozhen

LOCATION: Univ. of Arizona, Tucson, AZ, USA

DATE: 1996 PAGES: 136 pp. CODEN: DABBBB LANGUAGE: English CITATION:
Diss. Abstr. Int., B 1997, 58(2), 502 AVAIL: UMI, Order No. DA9720655

21/3,AB/69 (Item 6 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

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126184244 CA: 126(14)184244g DISSERTATION

Cellular and biochemical consequences of ornithine decarboxylase
regulation (polyamines, putrescine, apoptosis)

AUTHOR(S): Tome, Margaret Ellen

LOCATION: Univ. of Arizona, Tucson, AZ, USA

DATE: 1996 PAGES: 182 pp. CODEN: DABBBB LANGUAGE: English CITATION:
Diss. Abstr. Int., B 1997, 57(9), 5441 AVAIL: Univ. Microfilms Int., Order
No. DA9706691

21/3,AB/70 (Item 1 from file: 72)

DIALOG(R)File 72:EMBASE

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11782012 EMBASE No: 2002354357

The polyamine oxidase inactivator MDL 72527

Seiler N.; Duranton B.; Raul F.

N. Seiler, Laboratory of Nutritional Oncology, INSERM U-392, Inst. Rech.

Contre Can. 1^{er} App. Dig., 1, Place de l'Hopital, 67091 Strasbourg France

Progress in Drug Research (PROG. DRUG RES.) (Switzerland) 2002, 59/-

(1-40)

CODEN: FAZMA ISSN: 0071-786X

DOCUMENT TYPE: Journal ; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 120

Polyamine oxidase is a FAD-dependent amine oxidase, which is constitutively expressed in nearly all tissues of the vertebrate organism. In 1985, NSUP1, NSUP4-bis(2,3-butadienyl)-1,4-butanediamine (MDL 72527) was designed as a selective enzyme-activated irreversible inhibitor of polyamine oxidase (EC 1.5.3.11). It inactivates, at micromolar concentration and time-dependently, the enzyme in cells, as well as in all organs of experimental animals, without inhibiting other enzymes of polyamine metabolism. MDL 72527 served during nearly two decades as a unique tool in the elucidation of the physiological roles of polyamine oxidase. The compound has anticancer and contragestational effects, and it improves the anticancer effect of the ornithine decarboxylase inactivator (D,L)-2-(difluoromethyl)ornithine (DFMO). Profound depletion of the polyamine pools of tumour cells and effects on different components of the immune defence system are responsible for the anticancer effects of MDL 72527/DFMO combinations. Recently a direct cytotoxic effect of MDL 72527 at concentrations above those required for polyamine oxidase inactivation was observed. The induction of **apoptosis** by MDL 72527 was ascribed to its lysosomotropic properties. Therapeutic potentials of the apoptotic effect of MDL 72527 need to be explored. Polyamine oxidase is the last enzyme of the polyamine interconversion pathway that awaits the detailed elucidation of its structure and regulation. MDL 72527 should be useful as a lead in the development of inactivators which are selective for the isoforms of polyamine oxidase. Isozyme-selective inhibitors will give more profound insights into and reveal a diversity of specific functions of polyamine oxidase.

21/3,AB/71 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE
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11508455 EMBASE No: 2002080292
Rapid caspase-dependent cell death in cultured human breast cancer cells induced by the polyamine analogue NSUP1,NSUP11-diethylnorspermine
Hegardt C.; Johannsson O.T.; Oredsson S.M.
C. Hegardt, Department of Animal Physiology, Lund University, Helgonavagen 3B, SE-223 62 Lund Sweden
AUTHOR EMAIL: Cecilia.Hegardt@zoofys.lu.se
European Journal of Biochemistry (EUR. J. BIOCHEM.) (United Kingdom)
2002, 269/3 (1033-1039)
CODEN: EJBCA ISSN: 0014-2956
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 33

The spermine analogue NSUP1,NSUP11-diethylnorspermine (DENSPM) efficiently depletes the cellular pools of **putrescine**, spermidine and spermine by down-regulating the activity of the polyamine biosynthetic enzymes and up-regulating the activity of the catabolic enzyme spermidine/spermine NSUP1-acetyltransferase (SSAT). In the breast cancer cell line L56Br-C1, treatment with 10 μ M DENSPM induced SSAT activity 60 and 240-fold at 24 and 48 h after seeding, respectively, which resulted in polyamine depletion. Cell proliferation appeared to be totally inhibited and within 48 h of treatment, there was an extensive apoptotic response. Fifty percent of the cells were found in the sub-GSUB1 region, as determined by flow cytometry, and the presence of apoptotic nuclei was morphologically assessed by fluorescence microscopy. Caspase-3 and caspase-9 activities were significantly elevated 24 h after seeding. At 48 h after seeding, caspase-3 and caspase-9 activities were further elevated and at this time point a significant activation of caspase-8 was also found. The DENSPM-induced cell death was dependent on the activation of the caspases as it was inhibited by the general caspase inhibitor Z-Val-Ala-Asp fluoromethyl ketone. The results are discussed in the light of the L56Br-C1 cells containing mutated BRCA1 and p53, two genes involved in DNA repair.

21/3,AB/72 (Item 3 from file: 72)
DIALOG(R)File 72:EMBASE
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10981607 EMBASE No: 2001021850
Terminally alkylated polyamine analogues as chemotherapeutic agents
Casero R.A. Jr.; Woster P.M.
Dr. P.M. Woster, Dept. of Pharmaceutical Sciences, 539 Shapero Hall, Wayne State University, Detroit, MI 48202 United States
AUTHOR EMAIL: woster@wizard.pharm.wayne.edu
Journal of Medicinal Chemistry (J. MED. CHEM.) (United States) 04 JAN 2001, 44/1 (1-26)
CODEN: JMCMA ISSN: 0022-2623
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 190

21/3,AB/73 (Item 4 from file: 72)
DIALOG(R)File 72:EMBASE
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10713294 EMBASE No: 2000202354
Apoptotic cells knock down macrophage function and help parasite growth
Lopes M.F.

M.F. Lopes, Federal University of Rio de Janeiro, Rio de Janeiro, RJ
21944-970 Brazil
Biomedicine and Pharmacotherapy (BIOMED. PHARMACOTHER.) (France) 2000
54/4 (220)
CODEN: BIPHE ISSN: 0753-3322
DOCUMENT TYPE: Journal; Note
LANGUAGE: ENGLISH

21/3,AB/74 (Item 5 from file: 72)
DIALOG(R)File 72:EMBASE
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10532998 EMBASE No: 1999417763
The MYC dualism in growth and death
Fuhrmann G.; Rosenberger G.; Grusch M.; Klein N.; Hofmann J.; Krupitza G.
G. Krupitza, Institute of Clinical Pathology, University of Vienna,
Wahringer Gurtel 18-20, A-1090 Vienna Austria
AUTHOR EMAIL: g.krupitza@akh-wien.ac.at
Mutation Research - Reviews in Mutation Research (MUTAT. RES. REV.
MUTAT. RES.) (Netherlands) 1999, 437/3 (205-217)
CODEN: MRRRF ISSN: 1383-5742
PUBLISHER ITEM IDENTIFIER: S1383574299000848
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 166

Over-expression of the transcription factor c-Myc immortalizes primary cells and transforms in co-operation with activated ras. Therefore, c-myc is considered a proto-oncogene. Since its discovery c-Myc has been shown to render cells growth factor independent, accelerates passage through G1 of the cell cycle, inhibits differentiation and elicits **apoptosis**. Whereas the effects on immortalization, proliferation and inhibition of differentiation are in conceivable accordance with gain of function, as it is defined for a proto-oncogene, its pro-apoptotic activity disables a straight forward explanation of the physiological role of c-Myc and suggests a highly complex contribution during development. The recent accomplishments in c-Myc research shed some light on the difficult regulatory network which keeps check on c-Myc activity such as by binding to proteins some of which are transcription factors for non-c-Myc targets. Moreover, it was shown that genes are targeted by c-Myc depending on the sequence of flanking regions adjacent to the E-box or in dependence on the availability of binding partners which is most probably specific to the cellular context. Cdc25A and ornithine decarboxylase, both described to be c-Myc targets, have been brought forward as downstream effectors in the induction of proliferation under serum rich conditions, or in the induction of **apoptosis** when serum factors are limited. These genes seem to be regulated by c-Myc in a cell type-specific manner. H-ferritin, IRP2 and telomerase are the most recently discovered direct targets of c-Myc. The regulation of H-ferritin and IRP2 might explain the potential of c-Myc to promote proliferation and the regulation of telomerase could be responsible for the immortalizing properties of c-Myc. In the future, H-ferritin and telomerase have to be analyzed whether or not these genes are also Myc targets in other cell systems. Although the intense research efforts regarding the function of c-Myc last already two decades the role of this gene is still enigmatic. Copyright (C) 1999 Elsevier Science B.V.

21/3,AB/75 (Item 6 from file: 72)
DIALOG(R)File 72:EMBASE
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07665933 EMBASE No: 1999146968
Statement of polyamines

LE POINT SUR LES POLYAMINES

Dandrifosse G.; Deloyer P.; Grandfils Ch.; Loret S.; Peulen O.;

Dandrifosse A.C.

Prof. G. Dandrifosse, Universite de Liege, Faculte de Medecine, Institut de Chimie, Sart Tilman, 4000 Liege Belgium

Revue Medicale de Liege (REV. MED. LIEGE) (Belgium) 1999, 54/3 (175-183)

CODEN: RMLIA ISSN: 0035-3663

DOCUMENT TYPE: Journal; Article

LANGUAGE: FRENCH SUMMARY LANGUAGE: ENGLISH; FRENCH

NUMBER OF REFERENCES: 29

Polyamines are ubiquitous substances. Their intracellular concentration is controlled quickly and rigorously by extremely sophisticated systems. It depends on metabolism and cellular permeability. Polyamines act as structural and functional elements in the cell (nucleic acid conformation, cytoskeleton, radioprotection, **apoptosis**, proliferation and differentiation of cells...). They also play a role in various diseases (origin of food allergy, cancers...). They present a great therapeutic interest (oncology, molecular transfer to cell nucleus, transfer across the blood-brain barrier, parasitosis, effects on NMDA and GABA receptors in the central nervous system...).

21/3,AB/76 (Item 7 from file: 72)

DIALOG(R)File 72:EMBASE

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07555626 EMBASE No: 1999043546

Ornithine decarboxylase and cancer

Kubota S.

S. Kubota, Physiological Chem./Metabolism Dept., Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 Japan

AUTHOR EMAIL: kubota@bio.m.u-tokyo.ac.jp

Cancer Journal (CANCER J.) (France) 1998, 11/6 (294-297)

CODEN: CANJE ISSN: 0765-7846

DOCUMENT TYPE: Journal; Review

LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 20

21/3,AB/77 (Item 8 from file: 72)

DIALOG(R)File 72:EMBASE

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07398546 EMBASE No: 1998309010

Structural specificity of polyamines and polyamine analogues in the protection of DNA from strand breaks induced by reactive oxygen species

Chol Ha H.; Yager J.D.; Woster P.A.; Casero R.A. Jr.

R.A. Casero Jr., Johns Hopkins Oncology Center, Research Laboratories, 424 N. Bond St., Baltimore, MD 21231 United States

AUTHOR EMAIL: casero@welchlink.welch.jhu.edu

Biochemical and Biophysical Research Communications (BIOCHEM. BIOPHYS. RES. COMMUN.) (United States) 06 MAR 1998, 244/1 (298-303)

CODEN: BBRCA ISSN: 0006-291X

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 43

Reactive oxygen species are known to induce strand breaks and/or base modifications in DNA. DNA strand breaks are associated with many pathologies and programmed cell death. We have examined the ability of the polyamines and their analogues to protect phiX-174 plasmid DNA from strand

breakage induced by a oxygen-radical generating system. Spermine and several unsymmetrically substituted polyamine analogues reduced the amount of strand breakage at a physiologically relevant concentration of 1 mM. However, **putrescine**, spermidine, Nsup 1-acetylspermine, Nsup 1-acetylspermidine and symmetrically alkylated polyamine analogues were not able to reduce strand breakage at the same concentration. Thus, the unsymmetrically alkylated polyamine analogues and natural spermine can protect DNA against strand breakage induced by Cu(II)/Hinf 2Oinf 2 generated ROS similar to other more classical antioxidants.

21/3,AB/78 (Item 9 from file: 72)
DIALOG(R)File 72:EMBASE
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07131213 EMBASE No: 1998018798
Polyamines may regulate S-phase progression but not the dynamic changes of chromatin during the cell cycle
Laitinen J.; Stenius K.; Eloranta T.O.; Holtta E.
J. Laitinen, Department of Pathology, Haartman Institute, University of Helsinki, P.O. Box 21, FIN-00014 Helsinki Finland
AUTHOR EMAIL: jens.laitinen@helsinki.fi
Journal of Cellular Biochemistry (J. CELL. BIOCHEM.) (United States)
1998, 68/2 (200-212)
CODEN: JCEBD ISSN: 0730-2312
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 57

Several studies suggest that polyamines may stabilize chromatin and play a role in its structural alterations. In line with this idea, we found here by chromatin precipitation and micrococcal nuclease (MNase) digestion analyses, that spermidine and spermine stabilize or condense the nucleosomal organization of chromatin in vitro. We then investigated the possible physiological role of polyamines in the nucleosomal organization of chromatin during the cell cycle in Chinese hamster ovary (CHO) cells deficient in ornithine decarboxylase (ODC) activity. An extended polyamine deprivation (for 4 days) was found to arrest 70% of the odcsup - cells in S phase. MNase digestion analyses revealed that these cells have a highly loosened and destabilized nucleosomal organization. However, no marked difference in the chromatin structure was detected between the control and polyamine-depleted cells following the synchronization of the cells at the S-phase. We also show in synchronized cells that polyamine deprivation retards the traverse of the cells through the S phase already in the first cell cycle. Depletion of polyamines had no significant effect on the nucleosomal organization of chromatin in Ginf 1-early S. The polyamine-deprived cells were also capable of condensing the nucleosomal organization of chromatin in the S/Ginf 2 phase of the cell cycle. These data indicate that polyamines do not regulate the chromatin condensation state during the cell cycle, although they might have some stabilizing effect on the chromatin structure. Polyamines may, however, play an important role in the control of S-phase progression.

21/3,AB/79 (Item 10 from file: 72)
DIALOG(R)File 72:EMBASE
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07076742 EMBASE No: 1997358605
Association of dexamethasone-induced **apoptosis** and Ginf 1-arrest of human leukemic CEM cells with polyamine deficit
Choi S.-H.; Lee J.-A.; Chae Y.-S.; Min B.-H.; Chun Y.-S.; Chun B.-G.
B.-G. Chun, Department of Pharmacology, Korea University College of Medicine, Seoul 136-705 South Korea

Korean Journal of Physiology and Pharmacology (KOREAN J. PHYSIOL.
PHARMACOL.) (South Korea) 1997, 1/4 (457-466)
CODEN: KJPPF ISSN: 1226-4512
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 55

The effects of DFMO or/and **putrescine** on the dexamethasone-induced **apoptosis** of CEM cells were studied to investigate the role of polyamines in anti-leukemic glucocorticoid action. Dexamethasone-induced **apoptosis** was preceded by significant decreases of cellular polyamine contents and **putrescine** uptake activity. But DFMO produced decreases of **putrescine** and spermidine contents and marked increase of **putrescine** uptake activity, but did not induce **apoptosis**. However, dexamethasone and DFMO, respectively, induced Ginf 1-arrest in cell cycle and hypophosphorylation of pRb, resulting in the increase of Ginf 1 to S ratio and decrease of CEM cell count. DFMO enhanced the dexamethasone-induced **apoptosis** and Ginf 1-arrest. On the other hand, **putrescine** little affected the apoptotic and Ginf 1-arresting activities of dexamethasone, but almost suppress the effects of DFMO and also the DFMO- dependent enhancement of dexamethasone effects. These results suggested that the dexamethasone-induced **apoptosis** to be associated with pRb hypophosphorylation and Ginf 1-arrest in CEM cells might be ascribed to the concomitant decreases of cellular polyamine contents and **putrescine** uptake activity.

21/3,AB/80 (Item 11 from file: 72)
DIALOG(R)File 72:EMBASE
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05731144 EMBASE No: 1994133844
Oxidative stress and **apoptosis** in HIV infection. A role for plant-derived metabolites with synergistic antioxidant activity
Greenspan H.C.; Aruoma O.I.
LGD Biomedical Group, 23 Spring Hill Road, Annandale, NJ 08801 United States
Immunology Today (IMMUNOL. TODAY) (United Kingdom) 1994, 15/5
(209-213)
CODEN: IMTOD ISSN: 0167-5699
DOCUMENT TYPE: Journal; Short Survey
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The cascade of events resulting from 'oxidative stress' is markedly similar to that which can initiate **apoptosis**, a possible mechanism of immune-cell loss in patients with HIV infection and AIDS. Since primary and secondary metabolites found in plants can act as synergistic antioxidants, and can prevent oxidation-induced cell death, Howard Greenspan and Okezie Aruoma ask whether or not these compounds can be useful in inhibiting viral activation and the death of immune cells in HIV/AIDS.

21/3,AB/81 (Item 12 from file: 72)
DIALOG(R)File 72:EMBASE
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05618800 EMBASE No: 1994032051
Cellular transglutaminases in neural development
Hand D.; Perry M.J.M.; Haynes L.W.
Department of Zoology, University of Bristol, Woodland Road, Bristol BS8 1UG United Kingdom
International Journal of Developmental Neuroscience (INT. J. DEV. NEUROSCI.) (United Kingdom) 1993, 11/6 (709-720)
CODEN: IJDNND ISSN: 0736-5748

Enzymes of the transglutaminase family catalyze the Casup 2sup +dependent covalent cross-linking of peptide-bound glutamine residues of proteins and glycoproteins to the epsilon-amino group of lysine residues to create inter- or intramolecular isopeptide bonds. Transglutaminases can also covalently link a variety of primary amines to peptide-bound glutamine residues giving rise to two possibilities; firstly, where the primary amine has two or more amine groups, further catalysis can result in the formation of cross-linked bridges between glutamine residues, and secondly, where the primary amine is a monoamine, glutamine residues are rendered inert to further modification. The products are therefore in the main, homo- or heterodimers, or extensive, metabolically-stable multimeric complexes or matrices. Casup 2sup +dependent transglutaminase activity is present in the mammalian peripheral and central nervous systems and transglutaminase-catalyzed cross-linking of endogenous substrates has been demonstrated in neurons of Aplysia and the mammalian brain. Transglutaminase activity increases in the brain during development, principally owing to the increasing preponderance of glial cell activity. In a few regions including the cerebellar cortex, activity is also high in early development. Cellular transglutaminases occur widely in differentiating cells and tissues in mammals, with more than one transglutaminase frequently associated with a single cell type. The primary protein sequences of three cellular transglutaminases have been fully determined in different species, together with that of a mammalian protein homologue (band 4.2) which shares extensive sequence homologies with transglutaminases, but lacks the active site cysteine residue. The upstream sequences of two mammalian cellular transglutaminase genes (C and K) contain numerous regulatory sites, and an invertebrate transglutaminase, annulin, is spatially regulated within homeodomains. Multiple molecular forms of transglutaminase C and possibly other cellular transglutaminases exist in mammalian brain. The emerging picture is one of a family of cytosolic and membrane-bound proteins central to several regulatory pathways whose functions is to stabilize the cellular and intercellular superstructure in growing organisms. The targeted formation of glu-lys isopeptide bonds between proteins is central to this function. Cytoskeletal proteins, membrane-associated receptors, enzymes in signal transduction pathways and extracellular glycoproteins are candidate substrates as are polyamines, but few cellular proteins have been identified as components of naturally-occurring covalently-bonded matrices. Transglutaminases participate in the programme of neuronal differentiation in some but not all classes of neurone. Both neuronal and non-neuronal expression of transglutaminases may be important for guidance of migrating neurons or growth cones and sustainment of cell shape and coordinates during development. Cross-linking reactions may induce receptor clustering and amplify signalling pathways. Finally, in some forms of programmed cell death, expression of high levels of transglutaminase may play a part in cytological degeneration and **apoptosis**.

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S6	462	S2 AND PY>2001
S7	4	S6 AND EIF5A
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S9	4426	S3 AND (ADMINISTER? OR TREAT?)
S10	148	S9 AND APOPTOSIS?
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S18	19704	S17 NOT S10
S19	19682	S18 NOT S14
S20	202	S19 AND APOPTOSIS?
S21	81	RD (unique items)
S22	19560	S2 NOT S20

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File 155:MEDLINE(R) 1966-2002/Oct W3

*File 155: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.

File 5:Biosis Previews(R) 1969-2002/Oct W3

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*File 5: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.

Set Items Description

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E5	1	AU=TAYLOR CATHERINE ANN
E6	2	AU=TAYLOR CATHERINE E
E7	5	AU=TAYLOR CATHERINE J
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 E9 5 AU=WANG TZER CHUAN
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E12 8 AU=THOMPSON JOHN M D

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? s e1-e6

96 AU=THOMPSON JOHN
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133616 APOPTOSIS

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S20 10 RD (unique items)

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10 S20

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? t s20/3,ab/all

20/3,AB/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13384546 22125829 PMID: 12127120

Ligand activation of alternatively spliced fibroblast growth factor receptor-1 modulates pancreatic adenocarcinoma cell malignancy.

Vickers Selwyn M; Huang Zhi Qiang; MacMillan-Crow LeAnn; Greendorfer Jessica S; Thompson John A

Department of Surgery, University of Alabama at Birmingham, Birmingham, AL, USA

Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract (United States) Jul-Aug 2002; 6 (4) p546-53, ISSN 1091-255X Journal Code: 9706084

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Pancreatic adenocarcinoma continues to be a devastating tumor (28,000 new cases per year in the United States; 10% 2-year survival). Pancreatic adenocarcinoma frequently (90% of the time) overexpresses fibroblast growth factor ligands (FGF-1 and FGF-2) and alternatively spliced high-affinity receptors (FGFR-1beta) (FGFR-1alpha was previously found in normal pancreatic tissue). To study the significance of this observation in vitro, PANC-1 cells were stably transfected via the pMEXneo vector containing FGFR-1alpha (PANC-1alpha) or FGFR-1beta (PANC-1beta) isoforms. Cells were treated with 1 mg/ml of 5-fluorouracil. Cells were evaluated for growth inhibition, apoptosis (propidium iodide staining and flow cytometry, caspase 3 activation) and for Bcl-x(L)/BAX expression (by Western blot analysis). In vivo, 7 x 10(6) cells of each isoform were injected into nude Balb/c mice for xenograft formation (N = 10). Compared to PANC-1beta (9%) in vitro, 5-fluorouracil-induced death was significantly (P < 0.05) increased in PANC-1alpha (20%) at 24 hours. Increased cell death in PANC-1alpha was mediated by activated caspase 3 and was correlated with decreased expression of Bcl-x(L)/BAX. In vivo, PANC-1beta readily demonstrated formation of tumor xenograft at 2 weeks, whereas PANC-1alpha did not form tumors. Alternative splicing of FGFR-1 to the beta isoform appears to correlate with pancreatic adenocarcinoma cell growth in vivo and

resistance to chemotherapy. Inhibition of FGFR-1 splicing or overexpression of FGFR-1alpha inhibits pancreatic adenocarcinoma cell growth in vivo and restores cytotoxic responses to chemotherapy, thereby suggesting the basis of rational interventional strategies for this devastating tumor. (J GASTROINTEST SURG 2002;6:546-553)

20/3,AB/2 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
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12996830 BIOSIS NO.: 200100203979

Acidic fibroblast growth factor attenuates the cytotoxic effects of peroxynitrite in primary human osteoblast precursors.

AUTHOR: Reiff Donald A(a); Kelpke Stacey; Rue Loring III; Thompson John

A

AUTHOR ADDRESS: (a)1922 7th Ave. South, Kracke Building 120, Birmingham, AL, 35294-0016: Donald.Reiff@ccc.uab.edu**USA

JOURNAL: Journal of Trauma Injury Infection and Critical Care 50 (3):p 433-439 March, 2001

MEDIUM: print

ISSN: 1079-6061

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Background: Skeletal injury and associated ischemia and inflammation induce the generation of pro-oxidants such as peroxynitrite (ONOO-), which has been demonstrated to induce **apoptosis** in several cell lines. Fibroblast growth factor (FGF-1) is important for coordinating osteogenesis and angiogenesis of osseous repair. In vitro studies were performed examining the effect of FGF-1 on human osteoblast progenitor stromal stem (HSS) cell proliferation, differentiation, and response to ONOO-. Methods: HSS cells were isolated and growth kinetics determined in the presence and absence of FGF-1. The effect of FGF-1 on HSS cell expression of osteoblast-specific osteopontin and osteocalcin mRNA and protein was examined by reverse transcriptase polymerase chain reaction and Western blot techniques. To determine the sensitivity of HSS cells to ONOO- in the absence and presence of FGF-1 pretreatment, cells were exposed to varying concentrations of the oxidant and examined for cell death using quantitative fluorescence staining with fluorescein diacetate and propidium diacetate. Results: Treatment of HSS cells with FGF-1 significantly enhanced cellular growth rates by 5 days (4.6 X 10⁵ cells/mL vs. 3.1 X 10⁵ cells/mL) and induced expression of both osteopontin and osteocalcin mRNA and protein. Exposure of HSS cells to ONOO- resulted in a dose- and time-dependent delayed cell death that was more characteristic of **apoptosis** than necrosis. Pretreatment of HSS cells with FGF-1 prevented ONOO- mediated **apoptosis**. Conclusion: In vitro, treatment of HSS cells with FGF-1 stimulates cell growth and induces expression of differentiation markers specific to osteoblasts. FGF-1 treatment renders osteoblast precursors resistant to the cytotoxic effects of ONOO-. These results suggest that FGF-1 promotes the progression of bone repair mechanisms by increasing the population of osteoblasts and imparting protection to the cell line from the hostile inflammatory environment.

2001

20/3,AB/3 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
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12604893 BIOSIS NO.: 200000358395

Carcinoembryonic antigen family members CEACAM6 and CEACAM7 are differentially expressed in normal tissues and oppositely deregulated in hyperplastic colorectal polyps and early adenomas.

AUTHOR: Schoelzel Stefan; Zimmermann Wolfgang; Schwarzkopf Georg; Grunert Fritz; Rogaczewski Brigitta; **Thompson John**(a)
AUTHOR ADDRESS: (a)Institute of Molecular Medicine and Cell Research,
University of Freiburg, Stefan-Meier-Strasse 8, D-79104, Freiburg**
Germany

JOURNAL: American Journal of Pathology 156 (2):p595-605 February, 2000

MEDIUM: print

ISSN: 0002-9440

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Four members of the carcinoembryonic antigen (CEA) family, CEA, CEACAM1 (BGP), CEACAM6 (NCA-50/90), and CEACAM7 (CGM2), are coexpressed in normal colorectal epithelia but are deregulated in colorectal cancers, where they could play a role in tumorigenesis. As a basis for functional studies, their expression patterns in normal tissues first need to be clarified. This is well documented for CEACAM1 and CEA but not for CEACAM6 or CEACAM7. We have now carried out immunohistochemical expression studies on 35 different organs, using CEACAM6-specific (9A6) and CEACAM7-specific (BAC2) monoclonal antibodies. CEACAM7 was only found on the apical surface of highly differentiated epithelial cells in the colorectal mucosa and on isolated ductal epithelial cells within the pancreas. CEACAM6 was expressed in granulocytes and epithelia from various organs. CEACAM6 and CEACAM7 expression correlated with **apoptosis** at the table region of the normal colon, and both were absent from highly proliferating cells at the base of colonic crypts. CEACAM6 revealed a broader expression zone in proliferating cells in hyperplastic polyps and adenomas compared with normal mucosa, whereas CEACAM7 was completely absent. Down-regulation of CEACAM7 and up-regulation of CEACAM6 expression in hyperplastic polyps and early adenomas represent some of the earliest observable molecular events leading to colorectal tumors.

2000

20/3,AB/4 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
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12333449 BIOSIS NO.: 200000086951

Activation of FGFR-1 isoforms differentially modulates endothelial cell response to peroxynitrite.

AUTHOR: Jiao Jing(a); Samit Jessica E(a); Spear Nathan(a); Zinn Kurt(a); **Thompson John A**(a)

AUTHOR ADDRESS: (a)University of Alabama at Birmingham, Birmingham, AL**USA

JOURNAL: Free Radical Biology & Medicine 27 (SUPPL. 1):pS78 1999

CONFERENCE/MEETING: 6th Annual Meeting of the Oxygen Society New Orleans, Louisiana, USA November 18-22, 1999

SPONSOR: The Oxygen Society

ISSN: 0891-5849

RECORD TYPE: Citation

LANGUAGE: English

1999

20/3,AB/5 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)

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12071243 BIOSIS NO.: 199900366092

Apoptosis and tumorigenesis in human cholangiocarcinoma cells:

Involvement of Fas/APO-1 (CD95) and Calmodulin.

AUTHOR: Pan George; Vickers Selwyn M; Pickens Allan; Phillips John O; Ying Weizhong; **Thompson John A**; Siegal Gene P; McDonald Jay M(a

AUTHOR ADDRESS: (a)Department of Pathology, University of Alabama at Birmingham, 701 South 19th Street, 509 LHRB, B**USA

JOURNAL: American Journal of Pathology 155 (1):p193-203 July, 1999

ISSN: 0002-9440

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: We have previously demonstrated that tamoxifen inhibits the growth of human cholangiocarcinoma cells in culture and inhibits tumor growth when cells are injected into nude mice. However, the mechanism of action of tamoxifen remains unknown. Here we demonstrate that tamoxifen and trifluoperazine, both potent calmodulin antagonists, induce **apoptosis** in vitro, probably acting via the Fas system, in human cholangiocarcinoma cells. Human cholangiocarcinoma cell lines heterogenously express Fas antigen on their surface. Fas-negative and Fas-positive surface-expressing cells were isolated, cloned, and cultured. Fas antibody, tamoxifen, and trifluoperazine induced dose-dependent **apoptosis** only in Fas-positive cells; Fas-negative cells were unaffected. Furthermore, **apoptosis** induced by tamoxifen in Fas-positive cells was blocked by an inhibitory Fas antibody. Tamoxifen was not acting through an anti-estrogenic mechanism, because neither Fas-negative nor Fas-positive cells expressed estrogen receptors and the pure anti-estrogen compound, ICI 182780, did not induce **apoptosis** in either cell line. Fas-negative cells, but not Fas-positive cells, were able to produce tumors when subcutaneously injected into nude mice. These findings suggest Fas may be a candidate oncogene involved in the pathogenesis of cholangiocarcinoma. Furthermore, the similarity between the proapoptotic effects of tamoxifen and trifluoperazine support an underlying molecular mechanism for Fas-mediated **apoptosis** that involves calmodulin.

1999

20/3,AB/6 (Item 5 from file: 5)

DIALOG(R)File 5: Biosis Previews(R)

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11808473 BIOSIS NO.: 199900054582

Selective induction of **apoptosis** in mouse and human lung epithelial cell lines by the tert-butyl hydroxylated metabolite of butylated hydroxytoluene: A proposed role in tumor promotion.

AUTHOR: Dwyer-Nield Lori D; **Thompson John A**; Peljak Gertraud; Squier

Margaret K T; Barker Tobias D; Parkinson Andrew; Cohen J John; Dinsdale David; Malkinson Alvin M(a

AUTHOR ADDRESS: (a)UCHSC, C-238, Sch. Pharm., 4200 E. 9th Ave., Denver, CO 80262**USA

JOURNAL: Toxicology 130 (2-3):p115-127 Sept. 15, 1998

ISSN: 0300-483X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Butylated hydroxytoluene (BHT) causes lung injury in mice and promotes tumor formation. Hydroxylation of a tert-butyl group on BHT to

yield the metabolite, 6-tert-butyl-2-(2'-(2'-hydroxymethyl)-propyl)-4-methylphenol (BHTOH), may be required. BHTOH is more potent than BHT on an equimolar basis in causing lung damage, enhancing lung tumor development, killing isolated bronchiolar non-ciliated Clara cells, and inhibiting lung epithelial gap junctional intercellular communication. One mechanism proposed for tumor promoting agents is selective cytotoxicity; killing normal cells allows uninhibited clonal expansion of neighboring initiated cells. We compared the abilities of BHT, BHTOH, and other BHT metabolites to kill non-tumorigenic and tumorigenic mouse and human lung cell lines, and examined the contribution of **apoptosis** to this cytotoxicity. These cells lack the cytochrome P450 2B isozyme necessary for converting BHT to BHTOH. BHTOH and 4-hydroperoxy-4-methyl-2,6-di-tert-butyl-2,5-cyclohexadienone (BHTOOH) were most toxic, BHT and 2,6-di-tert-butyl-1,4-benzoquinone (BHTQu) were less potent, and 4-methyl BHT metabolites that are not pneumotoxic were ineffective. BHTOH most strongly induced **apoptosis**, based on nuclear condensation and transmission electron microscopy. Non-tumorigenic cells were as susceptible to cell death as the neoplastic cell lines when **apoptosis** and necrosis are not distinguished, but more sensitive to BHTOH-induced **apoptosis**. An apoptotic mechanism may underlie the lung tumor promoting actions of BHTOH.

1998

20/3,AB/7 (Item 6 from file: 5)
 DIALOG(R)File 5:BIOSIS Previews(R)
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11618973 BIOSIS NO.: 199800400858

Enhancement of peroxynitrite-induced **apoptosis** in PC12 cells by fibroblast growth factor-1 and nerve growth factor requires p21 Ras activation and is suppressed by Bcl-2.

AUTHOR: Spear Nathan(a); Estevez Alvaro G; Johnson Gail V W; Bredesen Dale E; Thompson John A; Beckman Joseph S

AUTHOR ADDRESS: (a)Tinsley Harrison Tower 958, Univ. Ala. at Birmingham, 1900 University Boulevard, Birmingham, AL **USA

JOURNAL: Archives of Biochemistry and Biophysics 356 (1):p41-45 Aug. 1, 1998

ISSN: 0003-9861

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Extracellular trophic factors can regulate whether cells subjected to oxidative stress will survive to proliferate or else undergo cell death. We have previously shown that about 35% of undifferentiated PC12 cells undergo **apoptosis** 18 h after exposure to peroxynitrite and that pretreatment with nerve growth factor (NGF) protects PC12 cells through activation of phosphatidylinositol (PI) 3-kinase. In contrast, pretreatment with acidic fibroblast growth factor (FGF-1) approximately doubled **apoptosis**. We report here that NGF added immediately after peroxynitrite treatment no longer protected against **apoptosis**, but instead enhanced **apoptosis** to the same extent as FGF. We further investigated which signaling pathways were involved in increasing the level of **apoptosis**. Overexpression of Bcl-2 blocked the increased **apoptosis** caused by NGF and FGF-1, but Bcl-2 did not prevent the induction of **apoptosis** by peroxynitrite alone. The increase in **apoptosis** caused by the trophic factors was also blocked by the expression of a dominant negative p21Ras mutant. Activation of PI 3-kinase by NGF pretreatment completely protected against both the enhanced **apoptosis** induced by FGF-1 pretreatment and NGF posttreatment and the **apoptosis** induced by peroxynitrite alone. Our

results indicate that the enhancement of peroxynitrite-induced **apoptosis** caused by NGF and FGF-1 is dependent on the stimulation of a proapoptotic pathway involving p21Ras that can be suppressed by Bcl-2.

1998

20/3,AB/8 (Item 7 from file: 5)
DIALOG(R)File 5:BIOSIS Previews(R)
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10691521 BIOSIS NO.: 199799312666

Acidic fibroblast growth factor enhances peroxynitrite-induced **apoptosis** in primary murine fibroblasts.

AUTHOR: Shin Jordan T; Barbeito Luis; Macmillan-Crow Lee Ann; Beckman Joseph S; **Thompson John A**(a

AUTHOR ADDRESS: (a)752 Lyons-Harrison Res. Build., Univ. Alabama Birmingham, 701 S. 19th St., Birmingham, AL 35294**USA

JOURNAL: Archives of Biochemistry and Biophysics 335 (1):p32-41 1996

ISSN: 0003-9861

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Oxidative stress is considered a major mediator of **apoptosis** in several cellular systems. Peroxynitrite is a highly toxic oxidant formed by the reaction of nitric oxide with superoxide. Primary embryonic murine fibroblasts, exposed to 1 mM peroxynitrite, resulted in delayed cell death characterized by membrane blebbing, cytoplasmic shrinkage, nuclear condensation, and DNA fragmentation that were more characteristic of **apoptosis** than necrosis. In addition, both morphological alterations and DNA fragmentation were inhibited by the endonuclease inhibitor aurintricarboxylic acid. Pretreatment of fibroblasts with acidic fibroblast growth factor (FGF-1) markedly enhanced peroxynitrite-induced **apoptosis**, an observation restricted to immediate-early transcriptional and activated tyrosine phosphorylation processes. FGF-1 pretreatment had no modulatory effect on cell death elicited by other reactive oxygen species, suggesting that enhancement of **apoptosis** involves a unique relationship between peroxynitrite and the growth factor. Exposure of cells to peroxynitrite resulted in immediate tyrosine nitration of several polypeptides, including major targets with estimated molecular masses of 62, 68, and 77 kDa. Pretreatment with FGF-1 did not alter targets of peroxynitrite-mediated tyrosine nitration, but rather increased the total amount of this amino acid modification. Treatment with other reactive oxygen species failed to induce tyrosine nitration. Collectively, these efforts demonstrate that FGF-1 transiently renders primary fibroblasts more sensitive to peroxynitrite-induced **apoptosis**. In addition, results presented here predict a pivotal role for FGF-1 and peroxynitrite-induced cytotoxicity during the resolution of inflammation and repair processes in vivo.

1996

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Expression of a truncated FGF receptor results in defective lens development in transgenic mice.

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ABSTRACT: Members of the fibroblast growth factor (FGF) family are thought to initiate biological responses through the activation of cell surface receptors which must dimerize to transmit an intracellular signal. Mammalian lens epithelial cells respond to exogenous extracellular FGF, either in tissue culture or in transgenic mice, by initiating fiber cell differentiation. The role of FGF signalling in normal lens development was evaluated by lens-specific synthesis of a kinase-deficient FGF receptor type I (FGFR1) in transgenic mice. This truncated FGF receptor is thought to act as a dominant negative protein by heterodimerization with endogenous FGF receptors. The presence of transgenic mRNA in the lens was confirmed by *in situ* hybridization and by polymerase chain reaction amplification of reverse transcribed lens RNA (RT-PCR). The presence of transgenic protein was determined by Western blotting with antibodies to an extracellular domain of FGFR1. Three of four transgenic families expressing the truncated FGF receptor exhibited lens defects ranging from cataracts to severe microphthalmia. While the microphthalmic lenses displayed a normal pattern of differentiation-specific crystallin expression, the lens epithelial cells were reduced in number and the lens fiber cells displayed characteristics consistent with the induction of **apoptosis**. Our results support the view that FGF receptor signalling plays an essential role in normal lens biology.

1995

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Peroxynitrite-induced cytotoxicity in PC12 cells: Evidence for an apoptotic mechanism differentially modulated by neurotrophic factors.

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ABSTRACT: Peroxynitrite is a powerful oxidant formed by the near-diffusion-limited reaction of nitric oxide with superoxide. Large doses of peroxynitrite (gt 2 mM) resulted in rapid cell swelling and necrosis of undifferentiated PC12 cells. However, brief exposure to lower concentrations of peroxynitrite (EC-50 = 850 μ M) initially (3-4 h) caused minimal damage to low-density cultures. By 8 h, cytoplasmic shrinkage with nuclear condensation and fragmentation became increasingly evident. After 24 h, 36% of peroxynitrite-treated cells demonstrated these features associated with **apoptosis**. In addition, 46% of peroxynitrite-treated cells demonstrated DNA fragmentation (by terminal-deoxynucleotide transferase-mediated dUTP-digoxigenin nick end-labeling) after 7 h, which was inhibited by posttreatment with the endonuclease inhibitor aurintricarboxylic acid. Serum starvation also resulted in **apoptosis** in control cells (23%), the percentage of

which was not altered significantly by peroxynitrite treatment. Although peroxynitrite is known to be toxic to cells, the present study provides a first indication that peroxynitrite induces **apoptosis**. Furthermore, pretreatment of cells with nerve growth factor or insulin, but not epidermal growth factor, was protective against peroxynitrite-induced **apoptosis**. However, both acidic and basic fibroblast growth factors greatly increased peroxynitrite-initiated **apoptosis**, to 63 and 70%, respectively. Thus, specific trophic factors demonstrate differential regulation of peroxynitrite-induced **apoptosis** in vitro.